Prenatal diagnosis and outcomes of congenital Lower Urinary Tract Obstruction (LUTO) at Tygerberg Hospital Fetal Medicine Unit: an audit of 12 years

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Table of Contents

Declaration

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Abstract

Objective: To determine the frequency, etiology, survival and associated morbidity of prenatally detected Lower Urinary Tract Obstruction (LUTO) to predict outcome and guide prenatal counselling and management.

Methods: Retrospective record review of prenatal LUTO cases at the Tygerberg Hospital Fetal Medicine Unit between January 2003 and June 2014.

Results: A total of 75 prenatal LUTO cases were detected in 12 years, giving an approximate frequency of 1.2 per 10,000 births calculated over a 3 year period. The median gestation at diagnosis was 22.4 weeks. Prenatally 39 (52%) were classified as 'Isolated', 16 (21%) as 'Isolated with marker' and 20 (27%) as 'Complex'. Gender difference observed with predominance of males (60/68) (88%), male:female ratio 7.5:1. Males had predominantly 'Isolated LUTO' (n=36, 60%), and females 'Complex LUTO' (n=5, 63%). Survival outcomes included: TOP 26 (35%), IUD 1 (1%), Stillbirths 8 (11%), NND 12 (16%), Infant deaths 4 (5%), alive >1 year 16 (21%), Lost to follow-up/Unknown 8 (11%). The most common etiology was PUV (51%). Chromosomal aneuploidy was found in 9.3% (7/75), all in males, with Trisomy 21 the most common anomaly (4/7) (57%). Prenatal findings shown to be significantly associated with a 'Poor outcome' are bilateral renal cortex echogenic/cystic changes (p=0.029), anhydramnios (p=0.011) and pulmonary hypoplasia (p=0.003). Morbidity measures showed survivors beyond 1 year of age (n=16) had renal impairment (n=6, 37%), bladder dysfunction (n=4, 25%), recurrent UTI''s (n=9, 56%).

Conclusion: This study adds novel data on the burden and impact of congenital LUTO in a South African, developing country setting. It confirms high mortality and significant morbidity, and supports the predictive value of specific antenatal ultrasound findings. Recommendations for clinical practice include; systematic ultrasound examination for other major anomalies, including soft markers to better define the risk of underlying chromosomal anomalies, determination of gender and karyotyping. The overall poor prognosis makes extensive counselling of the parents essential, especially if detected late in pregnancy, and supports the development of standardised guidelines for congenital anomalies.

Abstrak

Doel: Om die frekwensie, etiologie, oorlewing en geassosieerde morbiditeit van voorgeboorte Laer Urinêre Obstruksie (LUO) te bepaal ten einde die finale uitkoms te voorspel en inligting vir voorgeboorte berading en hantering te bepaal.

Metode: Retrospektiewe rekord oorsig van voorgeboorte LUO gevalle by Tygerberg Hospitaal Fetale Medisyne Afdeling tussen Januarie 2003 en Junie 2014.

Resultate: Vyf en sewentig prenatale LUO gevalle is gediagnoseer in ‘n 12 jaar tydperk, met ‘n berekende frekwensie van 1.2 per 10,000 oor ‘n 3 jaar periode. Die mediane gestasie van diagnose was 22.4 weke. In die voorgeboorte tydperk is 39 (52%) gevalle as ‘Geisoleerd’ geklassifiseerd, 16 (21%) as ‘Geisoleerd met merker’ en 20 (27%) as ‘Kompleks’. Manlike geslag was die algemeenste waargeneem (60/68) (88%), met ‘n manlik:vroulik verhouding van 7.5:1. Manlike geslag het veral ‘Geisoleerde’ LUO’ gehad (n=36, 60%), en vroulike geslag ‘Kompleks’ (n=5, 63%). Uitkomste rakende oorlewing sluit in: Terminasies 26 (35%), Intrauteriene sterftes 1 (1%), Stilgeboortes 8 (11%), Neonatale sterftes 12 (16%), Baba sterftes 4 (5%), Oorleef>1 jaar 16 (21%), Onbekend 8 (11%). Die algemeenste etiologie was Pelviese Urethra Kleppe (51%). Chromosomale aneuploidie was gevind in 9.3% (7/75), almal manlik, met Trisomie 21 die mees algemeen (4/7) (57%). Voorgeboorte bevindings wat statisties geasosieerd was met ‘n ‘Swak uitkoms’ is bilaterale renale korteks egogene of sistiese veranderinge (p=0.029), anhidramnios (p=0.011), en pulmonale hipoplasie (p=0.003). Morbiditeit in oorlewendes> 1 jaar (n=16) sluit in; abnormale nier funksie n=6 (37%), enurese n=4 (25%), herhaalde blaasinfeksies n=9 (56%).

Gevolgtrekking: Die studie dra nuwe kennis by tot die bestaande literatuur aangaande die las en impak van kongenitale LUO in Suid Afrika, ‘n ontwikkelende land. Dit bevestig die hoë mortaliteit en morbiditeit, en steun die voorspellende waarde van spesifieke prenatale ultraklank bevindinge. Praktiese aanbevelings vir kliniese praktyk behels die volgende; sistematiese ultraklank ondersoek om ander major kongenitale afwykings uit te skakel, insluitende sagte merkers om die risiko vir ‘n onderliggende chromosomale afwyking te bepaal, asook geslag bepaling en kariotipering. Aangesien die prognose van LUO swak is, is berading van die ouers belangrik, veral as die diagnose laat in swangerskap gemaak word, en daarom moet daar gestandardiseerde riglyne rakende hantering van kongenitale afwykings ontwikkel word.

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List of Tables

List of Figures

List of Abbreviations

AVSD	Atrioventricular septal defect
EEC	Ectrodactyly-ectodermal dysplasia-clefting syndrome
ESRF	End stage renal failure
GA	Gestational age
GAD	Gestational age at diagnosis
GFR	Glomerular filtration rate
GIT	Gastro intestinal tract
HN	Hydronephrosis
ID	Infant death
IUD	Intra uterine death
LUTO	Lower urinary tract obstruction
MCA	Multiple congenital anomalies
PBS	Prune Belly Syndrome
PM	Postmortem
PPUV	Presumed Posterior urethral valve
PUV	Posterior urethral valve
RCOG	Royal College of Obstetrics and Gynaecology
SB	Stillbirth
TGA	Transposition of the great arteries
TOF	Tetralogy of Fallot
TOP	Termination of pregnancy
UA	Urethral atresia
UK	United Kingdom
US	Urethral stenosis
U/S	Ultrasound
UTI	Urinary tract infection
VAS	Vesicoamniotic shunt

1. INTRODUCTION

Congenital anomalies are a significant burden of disease in developing countries. With the currently decreasing child mortality from preventable diseases, congenital abnormalities will become a larger proportion of the general health burden [1]. Lower Urinary Tract Obstruction (LUTO) is one of the most common congenital renal tract anomalies. It represents a heterogeneous group of congenital urogenital anomalies caused by different etiologies which all cause bladder outlet obstruction and is associated with significant pre and postnatal mortality and morbidity.

LUTO can potentially be detected by ultrasonography during prenatal care and influence the management of pregnancy. Limited published statistics on congenital anomalies in South Africa and inaccuracies in the birth registry result in a void of information which could shape obstetric and paediatric care and management policies and direct resources more appropriately.

At Tygerberg Hospital, and even in South Africa at large, it is uncertain what the exact contribution of LUTO is to the general burden of congenital disease in the population and the specific proportions of the different etiologies. This study proposed to conduct a retrospective clinical record review to define the causes and outcomes of prenatally diagnosed Lower Urinary Tract Obstruction (LUTO) at the Tygerberg Hospital Fetal Ultrasound Unit. This information can be used to direct prenatal counselling and care to optimize the health outcomes of affected pregnancies.

2. LITERATURE REVIEW

2.1 Background

2.1.1 Definition

Lower urinary tract obstruction (LUTO) is defined as a congenital obstructive uropathy caused by different etiologies which all cause bladder outlet obstruction.

2.1.2 Prevalence

Limited data suggest LUTO has an estimated prevalence of 2.2 to 3.3 per 10 000 births [2,3,4]. Postmortem studies focussed on congenital anomalies have reported LUTO as the cause in 30% of renal tract anomalies [5].

2.1.3 Diagnosis

Prenatal diagnosis of LUTO is possible with ultrasound and presents as megacystis (enlarged bladder), hydronephrosis (unilateral or bilateral), dilated urethra (keyhole sign) and oligohydramnios [6]. The findings are dynamic and typically progress with increased gestational age, however the natural history is quite variable.

2.1.4 Etiologies

The three most prevalent etiologies of LUTO are posterior urethral valves (PUV), urethral atresia (UA) or stenosis (US) and prune belly syndrome (PBS) [3,6,7]. Other occasional causes such as a prolapsed ureterocoele, congenital megaurethra, anterior urethral diverticulum, syringocoele are much less frequent [7,8]. Cloacal plate dysgenesis, megacystis-microcolon syndrome and isolated megacystis can also mimic LUTO features on prenatal ultrasound, even if an anatomical obstruction is not always present [8]. There is a strong gender bias, with a greater proportion of affected males, mainly because of PUV in males. LUTO can be present as an isolated congenital anomaly as most often observed in males, but it can be associated with other anomalies [3].

PUV's

The variation in LUTO etiologies between males and females is likely explained by the embryological origins of the urethra. PUV is a membrane in the posterior urethra obstructing outflow of urine from the bladder. There are 4 different types of PUV's however they cannot be distinguished on prenatal ultrasound and does not alter management or outcome [8].

Urethral atresia and stenosis

Urethral atresia is the total obstruction of the prostatic urethra which is typically found in males and usually leads to poor outcome with almost certain mortality [9]. Urethral stenosis is a milder form caused by partial obstruction with resultant improved expected outcome [8].

Prune Belly Syndrome (PBS)

PBS can present in both genders, however with a higher proportion of males affected, and is characterized by loose abdominal wall skin with underlying muscle deficiency, megacystis and upper urinary tract dilatation and cryptorchidism in males [8]. There are various theories as to the cause of this condition, eg. arrest of lateral plate mesoderm, obstruction during a critical developmental stage or a functional obstruction in the prostatic urethra [8]. PBS can be associated with other anomalies such as gastrointestinal (GIT), cardiac, limb anomalies.

2.1.5 Isolated and Complex LUTO

Published studies on prenatal LUTO, define 'Isolated LUTO' as evidence of LUTO on ultrasound, in the absence of other ultrasound anomalies. PUV is by far the most common underlying cause of isolated LUTO and is typically identified in males without any additional ultrasound findings [10,11,12,13]. PUV'S account for up to 64% of all obstructive uropathy cases [14] For example, Al-Hazmi et al found that, in males, 75% had PUV's and only 3% of all PUV's had associated malformations [10].

'Complex LUTO' is defined in prevalence studies as ultrasound findings of LUTO with additional ultrasound findings suggestive of more complex underlying etiology. Females often have a complex LUTO anomaly, caused by cloacal plate dysgenesis or other complicated syndromic associations which will have additional morbidity implications [3,7]. A large study by Al-Hazmi found a very high rate of associated malformations in females compared to males, with 64% of females having associated malformations and no female had PUV [10].

2.1.6 Chromosomal association

There are specific genetic causes that can be associated with LUTO, for example chromosomal anomalies e.g. Trisomy 21 and Trisomy 18 [15]. Chromosomal aneuploidy is present in approximately 5% of LUTO diagnosis [3,15]. Trisomy 18 is the most common followed by Down syndrome, Turner and Trisomy 13. A gender difference for chromosomal anomalies was reported as more prevalent in males in a study by Al-Hazmi [10]. This finding has not been reported elsewhere. First trimester megacystis is specifically associated with a high risk of underlying chromosomal anomaly, with a chromosomal anomaly or other malformations found in up to 50% of cases [16]. Trisomy 13 and 18 is the most common chromosomal anomalies found in 1st trimester megacystis [7]. Congenital LUTO has also been

described in association with dysmorphic syndromes eg, Goldenhar, Townes-Brockes, VACTERL association [7].

2.1.7 Morbidity and mortality

Congenital LUTO is undoubtedly associated with a high mortality and morbidity, in contrast with unilateral upper urinary tract anomalies that usually have a favourable prognosis [14]. The literature report varied rates of perinatal mortality, from 50% to as high as 80-90% [9,16,17]. A poor outcome is generally the result of pulmonary hypoplasia and/or renal dysfunction. Animal models have studied the pathophysiologal effects of LUTO on a growing fetus to determine the reasons for the poor outcome, the generally accepted theory is described in Table1[18]. The factors that have been shown to determine the mortality and morbidity of LUTO are gender, the specific etiology, gestation at which detected, progression over time in gestation, and will be discussed in detail in the following section. Recent prenatal intervention approaches may improve the mortality however the associated morbidity increases with survival [15]. If the perinatal period is survived, LUTO anomalies are associated with a 25-39% risk of developing end-stage renal failure later in life. The need for a renal transplant remains high in survivors with LUTO, with this group accounting for up to 60% of all paediatric cases needing renal transplants [19].

Urinary tract pathology
• Urine outflow obstruction below the bladder leads to increased intravesical pressure
• Raised intravesical pressure prevents ureteral urine drainage into the bladder with eventual ureteral dilatation
• Eventually, if obstruction not relieved, leads to involvement of the kidneys with reflux hydronephrosis with pyelectasis and calyectasis.
• Progressive kidney damage is related to renal parenchyma compression, affecting the medulla and later also cortical areas.
• Compression leading to focal hypoxia cause fibrosis and abnormal tubular function with hypertonic urine.
• Late sign of obstruction is cystic dysplasia.
Other organ systems
• Decreased amniotic fluid as a consequence of bladder outflow obstruction and progressive renal dysfunction
• Compression of chest with resultant decreased chest wall movement and breathing leading to pulmonary hypoplasia
• Potter sequence with skeletal abnormalities
• Lax abdominal wall musculature

Table 1: *Pathophysiology and sequential findings of prenatal LUTO* [18]

2.1.8 Prenatal Ultrasound

The improvement of ultrasound technology and the practice of universal prenatal routine scanning have led to a dramatic increased detection of congenital anomalies such as LUTO [6,20]. Prenatal ultrasonography is a non-invasive and sensitive procedure which is able to detect up to 88% of urological malformations [3,6]. However it is not a very specific investigation and even if features of urethral obstruction are clearly present, ultrasound cannot reliably differentiate between the underlying causes [3]. Studies have reported different specificity values ranging from as low as 40% to as high as 80% [6,16]. Urinary tract dilatation can be detected by ultrasound from 11-14 weeks gestation, but the diagnosis of LUTO is typically made on a second trimester ultrasound [15,20]. A normal detail ultrasound at 20 weeks does not exclude a LUTO diagnosis, Anderson et al found that renal pelvis dilatation could be normal before 23 weeks in a fetus that had significant obstruction postnatally [21]. The amniotic fluid volume can be accurately assessed by prenatal ultrasound. Fetuses with LUTO also have are a higher rate of other structural defects such as neural tube and cardiac defects which can be detected by prenatal ultrasound [15]. However oligohydramnios and especially anhydramnios make detailed ultrasound assessment difficult and incomplete. The role of ultrasound in prognostication of LUTO will be discussed in section 2.2.3.

2.1.9 Introduction to management of prenatal LUTO

In view of the poor outcome, management of a case with a prenatal LUTO often includes the option of termination of pregnancy. To determine the extent of renal damage prenatally, an invasive prenatal procedure (vesicocentesis) involving fetal urine aspiration with biochemistry assessment to assess renal function, can be performed. The value of the information gained by a vesicocentesis has been studied in order to provide prognostic information that could guide management decisions, such as active management or offering a termination of pregnancy [14,22]. Fetal therapeutic interventions aimed at treating LUTO in utero by relieving the obstruction and preserving renal function are areas of keen research and are in use in clinical practice in major centres in Europe and North America in particular.

Prenatal therapeutic approaches that have been researched include repeated vesicocentesis, fetal vesicocostomy, vesicoamniotic shunt (VAS), fetal cystoscopy and laser ablation, fetal ureterostomy. Unfortunately many procedures have been associated with a high fetal and maternal mortality. Vesicocentesis can be performed at a specialized fetal assessment unit in South Africa. The vesicoamniotic shunt (VAS) is the most widely used therapeutic interventional procedure and involves the placement of a shunt in the fetal bladder to divert fetal urine from the obstructed bladder to the amniotic cavity. This temporary measure aims to relieve the pressure and prevent progressive irreversible renal parenchyma damage in utero and preserving lung growth until the obstruction can be relieved after birth

[8,15]. The debate on the overall evidence for benefit for these interventions is ongoing and will be discussed in more detail in the following section.

2.2 Publications in the literature

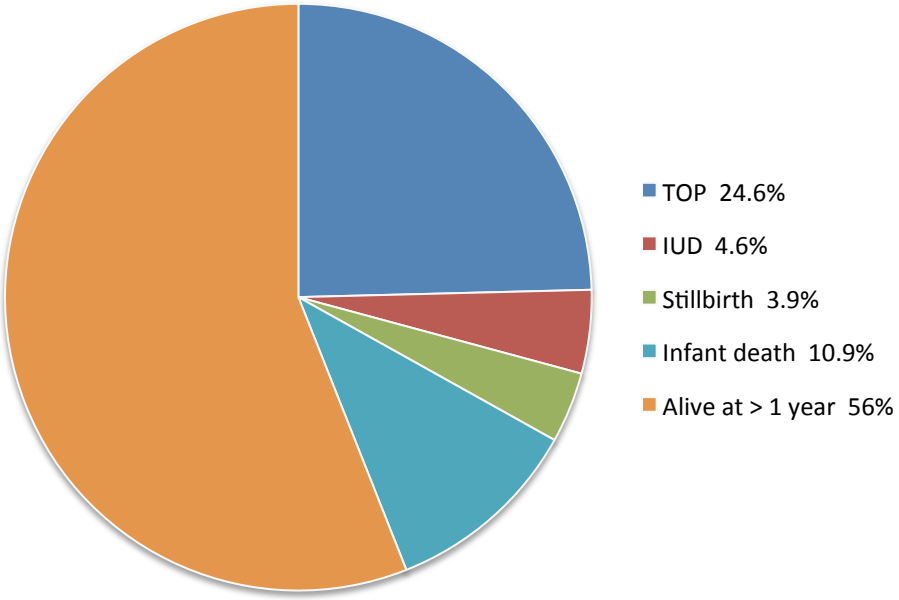
2.2.1 LUTO in the African context

There is no published data on the prevalence and presentation of LUTO in South Africa, and data derived from other populations is used to make management decisions. It is known that the frequency of specific congenital anomalies differs between different populations, due to reasons such as consanguinity, prenatal care practices, advanced maternal age, congenital infections, teratogen exposure and social deprivation [23]. There is limited available data on congenital anomalies in Africa, and tertiary centres striving for clinical excellence in a resource-limited setting have to do clinical audits to document the burden of disease in their setting. Odetunde et al did a retrospective study on PUV diagnosis and outcome at the University of Nigeria and provided valued new insight into postnatal LUTO in the African context [24]. All the affected individuals in the Nigerian study were male, and notably none was diagnosed prenatally. The study concluded that the high morbidity and mortality seen in their unit could be the result of late or missed diagnosis. A single case series which focussed solely on postmortem findings of prenatally detected LUTO and subsequent TOP was published by Van Velden et al from Tygerberg Hospital [25]. There are no publications detailing prenatal ultrasound characteristics of LUTO in Africa, and no studies investigating the outcomes of prenatally detected LUTO.

2.2.2 International LUTO studies

The early LUTO publications were descriptive studies, describing the different etiologies, the natural progression of LUTO in the prenatal and postnatal period, delineating postmortem findings, and reported a high morbidity and mortality [12,26]. With the advance of fetal interventions, there was some optimism that LUTO could potentially be a modifiable condition and amenable to prenatal therapy with improved longterm outcomes. Recent publications have focussed on the role of fetal interventions and have examined the evidence for their long-term benefit [17,27,28].

The largest population based study has been conducted in the United Kingdom (UK) by Malin et al and together with smaller centre-based studies have estimated the prevalence of LUTO anomalies - see Figure 1 [3].



- Prenatal diagnosis rate was 66 %
- Isolated LUTO 77.8% Complex LUTO 22.2%
- PUV 63% (Isolated 89% Complex 11%)
- UA/US 16.9% (Isolated 54% Complex 46%)
- PBS 2.5% (Isolated 29% Complex 71%))
- LUTO unspecified 17.6% (Isolated 66% Complex 34%))
- Chromosomal anomaly in 5.6% of all LUTO (In 25.4% of complex LUTO cases)
- Trisomies 13 (5.7%), 18 (9.6%), 21 (7.7%) & structural chromosomal rearrangements

Figure 1: *Summary of data from Malin et al 2012*[3]

2.2.3 Defining prenatal prognostic factors

The outcome of LUTO is dependent on the gender of fetus, time of onset of obstruction, the severity, and the total duration of obstruction [15]. The diagnostic challenge is to predict which fetus has a potential good outcome by identifying markers, either ultrasound or biochemical, to distinguish between groups with likely poor and good outcomes as early as possible.

The definitions referring to poor and good outcomes vary between publications thus making comparisons and pooling of data difficult. 'Early poor outcome' has a more consistent definition and is often defined by studies as fetal, neonatal and infant death, however a 'Late poor outcome' and a 'Good outcome' have a more wide interpretation between studies [10]. A 'good outcome' that may mainly refer to survival past a certain age, which could be between age 1 and 5 years, could still be associated with significant morbidity eg. multiple surgeries and hospitalizations, end stage renal failure with need for dialysis and renal transplant, permanent bladder instability with need for self-catheterization and enuresis. Even if the

renal function remains stable in childhood, longterm follow-up into adulthood shows that many progress to end-stage renal failure (ESRF) after puberty [13].

A meta-analysis of 13 publications concerning prenatal prognostic prediction of renal function concluded that the most specific qualitative ultrasound findings in the 2nd trimester are the liquor volume and the renal cortex appearance [29]. Chronic significant oligohydramnios in the second trimester is considered the most reliable prognostic ultrasound feature of poor outcome [29,30]. Increased renal cortex echogenicity or cystic parenchyma changes is also a promising sensitive (0.57) and specific (0.84) predictor of renal outcome as defined by serum creatinine >1.2mg/dl (106umol/L) at age 1 year [29]. The review concluded that the evidence for prognostic factors is limited due to the small numbers and heterogeneity between studies.

The severity of renal pelvis dilatation and fetal urine biochemistry measuring sodium and b2-macroglobulin (table 2) has also been studied as possible prognostic indicators of outcome [6,8,14]. A renal pelvis >15mm in any gestation is considered severe prenatal hydronephrosis [6]. Prenatal renal pelvis dilatation severity, as measured by renal pelvis AP diameter or subjective assessment, has not been shown to be statistically significant in predicting outcome of LUTO in the literature [29]. Clayton et al have published comprehensive descriptions of fetal ultrasound and vesicocentesis findings, detailing the different bladder shapes post vesicocentesis as a possible guide to the etiology of the LUTO [6,8].

Some authors consider that the underlying etiology determines the outcome more accurately than the specific ultrasound changes, however accurate distinction between etiologies is not possible prenatally [9,31,32].

Prenatal ultrasound findings predictors of renal failure in survivors	Studies reporting statistically significant findings
Gestation at diagnosis GA <24 weeks Oligohydramnios Renal Cortical Appearance	p=0.14 p=0.02 p=0.04 Meta-analysis by Morris at al 2009 [29]
Prenatal ultrasound findings predictors of normal renal function	Studies reporting statistically significant findings
Amniotic fluid normal	p =0.02 Sarhan et al 2008 [33]
Prenatal ultrasound findings predictors of fetal/perinatal death	Study reporting significant findings
Urine biochemistry: Na >100 mmol/L b2 –microglobulin >13mg/L (Lethal) > 6mg/L (Poor prognosis)	Lissauer et al 2007 [14]

Table 2: *Summary of prognostic indicators reported in the literature [14,29,33]*

2.2.4 Postmortem findings

Postmortem investigations have provided valuable insight into the specific underlying etiology causing the LUTO, as well as correlating the ultrasound images with actual structural changes [16]. Van Velden et al from Tygerberg Hospital described 9 postmortem examinations of LUTO cases at 18-24 weeks [25]. The article elaborated on the theory of the timing and type of urethral obstruction and the embryological origins as an explanation why some of the pressure effects can spontaneously improve in some cases. Table 3 has a summary of the findings. All cases had marked abdominal distention and a funnel shaped appearance of the prostatic urethra regardless of the etiology. The prostate in all cases showed a spectrum of hypoplasia or abnormal development. The bladder wall histology did not show a specific correlation to the etiology and degree of obstruction. The abdominal wall muscle showed abnormalities related to pressure atrophy.

Case	Gestation	Ultrasound	PM obstruction	Karyotype
1	22	Uropathy, pulmonary hypoplasia	Valve, incomplete obstruction	Not done
2	17	Uropathy, bil HN, pulmonary hypoplasia, oligohydramnios	No structural obstruction	46,XY
3	24	Uropathy, pulmonary hypoplasia, oligohydramnios	No structural obstruction	46,XY
4	21	Uropathy, pulmonary hypoplasia, oligohydramnios	No structural obstruction	Not done
5	18	Uropathy, club foot	Canalization defect	46,XY
6	20	Uropathy, oligohydramnios	Canalization defect	46,XY
7	23	Progressive uropathy, renal dysplasia	Neurofibrous band	46,XY
8	20	Uropathy, pulmonary hypoplasia, oligohydramnios	Canalization defect	46,XY
9	22	Uropathy, oligohydramnios	Valve, incomplete obstruction	Failed

Table 3: *Postmortem findings of Van Velden et al 1995* [25]

2.2.5 Prenatal versus postnatal diagnosis

Studies have shown conflicting opinions regarding whether prenatal diagnosis of LUTO has a superior outcome to postnatal detected LUTO, which may reflect the fact that prenatally

detected cases present the severest spectrum of obstruction [13,26]. The rationale for prenatal diagnosis is not solely to have the opportunity for a TOP or fetal intervention, but if LUTO is identified prenatally then early postnatal treatment in the case of PUV with intermediate severity of obstruction can lead to a reasonable outcome [13].

2.2.6 Prenatal interventions and therapies

The current evidence regarding the benefit of prenatal interventions such as vesicoamniotic shunts, in-utero percutaneous cystoscopy and hydro-ablation of PU valves as assessed by the randomised controlled PLUTO trial in the UK, as well as smaller mainly observational studies in the US and Europe have indicated that even if short-term survival is improved, that the survival is associated with significant morbidity [2,4,14,17,20,27,28]. Therefore the consensus is that the long-term prognosis for renal function is still unclear and therefore cases for these interventions need to be carefully selected, for details see Table 4 [18]. The risks of the procedure need also be considered, namely maternal or fetal infection and miscarriage risk, as well as reports of shunt blockage or dislodgement in up to 40% of cases [18,34,35].

Selecting candidates for fetal LUTO intervention

Ultrasound assessment

- Congenital anomalies eg cardiac, neural tube
- Karyotype (CVS if anhydramnios) (Female often have complex LUTO associated with cloacal abnormalities and does not benefit from in utero shunting)

Renal function

- Sequential vesicocentesis sampling 48-72 hour interval
- Urine biochemistry trend

Ideal candidate for VAS: normal male karyotype, progressively improving urine biochemistry, urine meets threshold parameters (below)

Upper threshold values fetal urine considered for prenatal intervention

Na <100 mmol/L

Cl <90 mmol/L

Osmolality<190mOsm/L

Ca <8mg/dL

B2 microglobulin< 6mg/L

Tot protein <40mg/dL

Table 4: *Selecting candidates for prenatal LUTO surgical intervention* [18]

2.2.7 Longterm outcomes and morbidity

Longterm outcomes after prenatal LUTO diagnosis have been studied, both with and without therapeutic prenatal interventions. These provide guidance to prenatal counselling of prospective parents and assist with immediate management decisions and longterm follow-up. Evans reports a survival of 91% after VAS, with 25% of survivors developed serious renal impairment and 15% required transplantation. He recommends a "carefully balanced approach in counselling" after prenatal LUTO diagnosis before embarking on interventions in order for families to make a personalized decision [18].

The longterm morbidity is related to both renal and bladder complications. Postnatal renal dysfunction can be measured by serum creatinine and glomerular filtration rate (GFR). A serum creatinine at 1 year has better predictive value than the initial level [36]. Table 5 below summarises the morbidity experienced by LUTO survivors, therefore longterm follow-up is recommended in all cases, even after successful treatment to relieve the obstruction [28]. The presence of LUTO is not associated with poor neurodevelopmental outcome despite intensive treatments like dialysis and renal transplants [37].

Morbidity	**Studies**
Renal failure	VAS survivors, 1/3 require dialysis and renal transplant [37] 17% had renal transplant at mean age 6.5 years [13] 70% ESRF at 11.3 years [38] 20% developed renal failure at mean age 4 yr [26] 30% PUV and 20% PBS develop ESRF by adolescence [8] Elevated creatinine in 36% of survivors [10]
Bladder – voiding dysfunction, including urinary incontinence after valve ablation	18% incontinent [33] 40% adult men, continent with detrusor weakness [28] 31% bladder instability [39]
Recurrent UTI	Increased, no percentage specified [12,19,26]
Male infertility	Increased if uremic)/PBS, no percentage specified [40]
Poor growth	Increased (if uremic), no percentage specified [37]
Ongoing musculoskeletal and respiratory problems	50% of LUTO treated by VAS [37]

Table 5*: Longterm morbidity of LUTO*

2.3 Ethics and Counselling

2.3.1 Ethics in the prenatal setting

Ethics relating to pregnancy is a vast field concerning many complex matters and disputes, some of which is relevant in LUTO in the prenatal setting. A number of pertinent points related to this study will be raised however a full disclosure of the topic is beyond the scope of this research report. Medical professionals are expected to uphold the four generally accepted ethical principles to ensure optimal care for their patients (Table 6). In the prenatal setting, after the diagnosis of a congenital anomaly eg. LUTO, balancing these principles can become quite complex – taking into account more than one patient (fetus and mother); uncertainty of ultrasound findings and expected outcome for the fetus; the rights of the fetus; termination of pregnancy; distributive justice dilemmas relating to access of care and cost-effective care [41]. Therefore clear guidelines and protocols are necessary to ensure ethical medical practice in the prenatal setting.

Ethical principles in medicine
• **Respect** for the **autonomy** of persons: respect patient self-determination, and protect vulnerable patients with diminished autonomy. • **Beneficence:** prioritize the welfare of patients, actively promoting their health. • **Non-maleficence**: "do no harm", avoid harm to patient, either preventing or minimizing harm • **Justice:** treat patients with fairness, ensure equity in distribution of benefits and burdens of health care as fairly as possible in a society

Table 6: *Ethical principles in medicine*

2.3.2 Termination of pregnancy

TOP after prenatal LUTO diagnosis

TOP is a frequent management option selected for a prenatal LUTO diagnosis, however the frequency shows a wide variation between studies. The decision to have TOP after prenatal LUTO diagnosis was respectively 60% and 24.6% in two UK studies [2,3]. French data showed a TOP rate of 48% and 55% for LUTO [10,42]. A US review over 20 years showed a TOP uptake in 46% of PUV cases [43]. There are no published detail on the gestation of TOP, and therefore limited data on late (>24 weeks) TOP's.

The increased use of ultrasonography has not changed the TOP rate in the US according to a study by Hsieh, however this may not be true for all populations as a French study did find a significant increase in TOP in parallel to increased ultrasound practice [42,43].

TOP legislation

In South Africa TOP's are regulated by the SA Choice on Termination of Pregnancy Act (1996) (Appendix D). According to the legislation a TOP could be offered for fetal anomaly or disability under the following circumstances: "*(b) from the 13th up to and including the 20th week of the gestation period if (ii) there exists a substantial risk that the fetus would suffer from a severe physical or mental abnormality; or (c) after the 20th week of the gestation period if the continued pregnancy (ii) would result in a severe malformation of the fetus."*

The wording of the clause is vague and open to interpretation as to the exact meaning of what constitutes a 'severe' abnormality or malformation. This ambiguity in TOP legislation is not unique to South African law.

The United Kingdom (UK) TOP act states: *"When a fetal abnormality has been detected, the pregnancy can be terminated before 24 weeks of gestation under Ground 1(1)(a) of the Abortion Act or 1(1)(d) Ground E', if there is a substantial risk that the child if born it would suffer from such physical or mental abnormalities as to be seriously handicapped"* [44]. As the UK law does not clarify what constitutes a 'substantial risk of serious handicap' or give guidance about severity, the Royal College of Obstetrics and Gynaecology (RCOG) in 1996 provided practical applications for decision-making [44]. They concluded that the 'severity' of an abnormality should be assessed in the following contexts:

"*1) the potential for effective treatment, either in utero or after birth*

2) on the part of the child, the probable degree of self-awareness and of ability to communicate with others, the suffering that would be experienced, the probability of being able to live alone and to be self-supportive as an adult,

3) on the part of society, the extent to which actions performed by individuals without disability that are essential for health would have to be provided by others" [44].

Ethics of late Termination of pregnancy (TOP)

The general trend of late prenatal booking and subsequent late prenatal ultrasound diagnosis of congenital anomalies, such as LUTO, contributes to the ethical burden that challenges a fetal assessment centre, as termination of pregnancy options late in a pregnancy includes feticide procedures. There are no national guidelines in South Africa to help interpret the South African TOP law which can be open to interpretation for late termination of pregnancy. Therefore the options and practice of late termination of pregnancy differ between clinical care facilities in South Africa and the onus is on the facility to practice irreproachable prenatal

care by developing their own guidelines, based on local population information, to assist with prenatal management decisions in a ethically moral and legally responsible manner.

A late termination of pregnancy is usually preceded by a feticide procedure, this is considered a humane intervention and a standard international practice which aims to minimize any potential suffering for the fetus. The South African law does not refer to feticide procedures or specify a specific gestation for feticide at all. The UK has specific guidelines published by the 1996 Royal College of Obstetricians and Gynaecologists and clarified in 2001 which is quoted below:

"For all terminations at gestational age of more than 21 weeks and 6 days, the method chosen should ensure that the fetus is born dead. This should be undertaken by an appropriately trained practitioner. Intracardiac potassium chloride is the recommended method and the dose should ensure that fetal asystole has been achieved" [45].

Publications such as Chervenak et al focus on the specific ethical principles involved in the feticide procedure, namely autonomy and beneficence and balancing these principles in different scenarios to provide practical guidance to clinicians [46]. Moodley discusses feticide in terms of the slippery slope arguments, eugenics and the moral status of the fetus and newborn and how disparities between late TOP policies between centres result in ethical and practical dilemmas, she then concludes *"It is hence imperative that all obstetricians and obstetric units – in public and private practices, have evidence-based protocols and policies in place. Such policies must consider the important concepts of fetal and neonatal moral status"* [47].

The Fetal Medicine Unit at Tygerberg has developed such a policy document to act as guideline for best practice at Tygerberg Hospital, namely the "The Policy on late termination of pregnancy (TOP) for fetal anomalies" (unpublished data). This policy document was developed in collaboration with multiple stakeholders (obstetrics, genetics, and paediatrics) and has been reviewed by ethics experts and the Tygerberg Hospital Board. This practical guideline addresses the possible indications for late TOP in cases with prenatally detected fetal anomalies by using 4 categories clearly distinguishable on ethical principles, with a list of example anomalies to be used as a reference guide, using an approach similar to the RCOG 1996 guidelines.

According the Tygerberg Hospital Policy document, late TOP should be offered only where the fetal condition is such that there is near certainty (estimated 80-90% chance) that the fetal outcome will include one or more of the following: early death; profound and irreversible deficit in developmental capacity; unbearable pain and suffering; unreasonable burden of care. Better understanding of LUTO outcomes and prognostic factors in local circumstances will improve the accuracy of decisions regarding the offer of TOP or late TOP for LUTO.

2.3.3 Counselling

There are several emotional and ethical issues raised by prenatal fetal pathology and the role of adequate counselling explaining the underlying pathology, likely outcome, potential for intervention, long-term prognosis, likely genetic risk and recurrence, implies that a considerable amount of information needs to be clearly communicated to the family to enable them to make a family values-based decision in keeping with their value system and still abide by ethical, moral and upholding legislative principles. To enable prospective parents to make informed choices about the future of a pregnancy requires comprehensive knowledge of the possible causes and outcomes of a condition.

There is an important role for genetic counselling in prenatal anomaly diagnoses, both in the determination of the likely underlying pathology and the likeliness of a genetic condition and the need for specific investigations. Genetic counselling is defined as:

"the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:
• Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
• Education about inheritance, testing, management, prevention, resources and research.
• Counseling to promote informed choices and adaptation to the risk or condition." [48]

Genetic counsellors are particularly adept at counselling in a prenatal setting, as their skills include presenting information in a clear way in understandable language, familiarity with dealing with explaining risks and uncertain or ambiguous information and results, facilitate decision-making, addressing psychological issues, recognizing pathological grief and familiarity with ethical dilemmas. The empathic non-judgemental approach adopted in a genetic counselling session can be valuable in a complex emotional counselling session after a fetal anomaly with a poor prognosis, such as LUTO, has been identified. Table 7 presents the general principles and ethos of genetic counselling as discussed in Uhlmann et al [49].

Principles of genetic counselling (based on Carl Rogers' theory)
Base on principles of non-directiveness and client-centered approach.

- Non-directiveness (no direct guidance, but facilitate client to process information and make personal decision congruent with their belief systems and values)
- Client-centered (promoting patient autonomy and empowerment)

continued

Ethos of genetic counselling
• Voluntary utilization of services
• Equal access
• Complete disclosure of information
• Client education
• Non-directive counselling
• Attention to psychosocial and affective dimensions in counselling
• Confidentiality and protection of privacy

Table 7: *Genetic counselling principles* [49]

2.4 Protocols and the role of clinical record reviews

2.4.1 Management protocols in the literature

Practical guidelines in the form of prenatal management protocols have been published (Tonni 2013 et al [20]) (Appendix C) (Smith-Harrison 2015 et al [50]) (Appendix D). These publications aimed to guide the diagnostic process including evaluation and selection for intervention and direct the difficult prenatal counselling about likely prognostic outcome, specifically to provide clear guidance for clinicians and facilitate the difficult decision process for parents.

2.4.2 Clinical record review

Current rapid developing technology ensures improved diagnostic capability and constant review of treatment practices. It is therefore important to keep up to date to ensure optimal care. However it is challenging to plan for optimal service delivery if no local data on actual number of cases and their respective outcomes are available. A clinical record audit is essential to ensure continuous quality control in a clinical unit. This process can then lead to the development of local evidence-based guidelines which can result in the improvement of clinical care in context.

2.5 Local setting and policies

At the Tygerberg Hospital Fetal Medicine Unit trained experienced genetic counsellors are part of the fetal medicine obstetric team and can ensure continued care and support prenatal and postnatal. Liaison with paediatrics and surgeons at regular SNAG meetings ensure continuity of care as well as providing outcome information in individual cases. The detailed policy guideline to late TOP that has been discussed above is used on a daily basis to determine who would be offered a late TOP. In a situation where the policy does not clearly

direct a course of action, an urgent ethics meeting can be convened, consisting of various members of the hospital ethics committee and the attending physicians. The aim is to provide a standardised ethically and morally sound level of care to all patients.

2.6 Conclusion

The published information on LUTO presents largely European and North American population data, and most studies consists of small numbers. Currently, due to a paucity of other information, this data is used and extrapolated to other populations in order to provide some benchmarks and guidance. More global information is needed about prevalence, ultrasound predictive factors, success of prenatal intervention, longterm renal outcome of survivors. This research aims to review the presentation and outcome of fetuses that had been diagnosed with features of LUTO in a tertiary referral fetal ultrasound unit with the aim of delineating current experience and to inform future practice.

3. AIMS AND OBJECTIVES

The aim of this study was to determine the frequency of fetal Lower Urinary Tract Obstruction (LUTO) anomalies at the Tygerberg Fetal Medicine Unit based at Tygerberg Hospital, and to characterize the specific underlying causes/ pathology identified as well as define the outcomes and associated morbidity of all known cases.

The objectives were:

(1) to determine the frequency of all prenatally diagnosed Lower Urinary Tract Obstruction (LUTO) at the Tygerberg Fetal Medicine Unit and compare this with those of other populations where data is available and look at trends over time

(2) to determine the mean gestational age of prenatal ultrasound detection

(3) to determine the percentage of isolated versus complex anomalies

(4) to determine the specific underlying causes/ etiology

(5) to determine the frequency of chromosomal abnormalities detected in cases of isolated and complex LUTO

(6) to define the outcomes in terms of survival and morbidity

(7) to determine prenatal ultrasound prognostic indicators

4. METHODS

4.1 Study design

The study was a retrospective review of clinical records.

4.2 Setting and study population

The study was conducted at Tygerberg Hospital. The study-group included all patients who attended the Fetal Medicine Unit at Tygerberg Hospital between January 2003 and June 2014, and had prenatal ultrasound findings consistent with LUTO.

4.3 Eligibility

Relevant cases were identified by searching the Fetal Medicine Unit ASTRAIA database. This database contains all the prenatal ultrasound assessments performed at the unit since 2003 and prospectively entered at the time of the examination. The case definition of LUTO/obstructive uropathy for this study was defined as ultrasound evidence of a dilated bladder with upper urinary tract dilatation.

4.4 Ethics

Ethical approval was obtained from the Human Research Ethics Committee of the University of Stellenbosch (protocol nr. N13/06/081) as well as from the review board at Tygerberg Hospital. Patient privacy was protected and confidentiality maintained as all data obtained from clinical records were de-identified by using a specific study number instead of names or surnames. A waiver of informed consent was granted by the Ethics review board as the study only involves a retrospective review of clinical records.

Risks and benefits

Risks - We did not anticipate any risks to our study population.

Benefits - The anticipated benefits of this study will be the development of evidence-based guidelines to improve patient care at the Fetal Medicine Unit, Tygerberg Hospital. The information and figures derived from this research enable the service to target resources appropriately and cost effectively, by taking into account the number of estimated cases expected per annum and guide further investigations in both a practical and economical manner. The data on associated morbidity and specific outcomes in a local setting is vital to update and inform genetic counselling information and practices which would allow parents access to valid information in order to make autonomous informed decisions.

4.5 Data collection

Ultrasound details, genetic counselling information, maternal and infant (if applicable) clinical records were retrieved from Medical Records at Tygerberg Hospital. Patient privacy was protected and confidentiality maintained as all data obtained from clinical records was de-identified by using a specific study number in the place of names or surnames.

Relevant data was collected and entered into an Excel database by the researcher, with a study code as identifier. The database was stored on a computer that is protected with a password. To confirm accuracy, all data entries were double-checked by the researcher. All identifying information was kept in a locked office at the University of Stellenbosch, Tygerberg campus.

4.5.1 Prenatal data

Data on fetal biometry and LUTO ultrasound findings were recorded with the following specific points.

- For the fetal bladder - 'keyhole sign' indicative of a posterior urethral dilatation, the size and bladder wall thickness were noted and megacystis defined as an enlarged bladder with failure to empty during the duration of the ultrasound examination.
- For the kidneys – Unilateral or bilateral involvement. Degree of hydronephrosis was graded as mild (<10mm), moderate (10-19 mm) and severe (≥20 mm) renal pelvis dilation in 2nd trimester. Renal cortex was described as normal, echogenic or cystic.
- The presence of urethral and ureteral dilatation was noted.
- Amniotic fluid noted as normal, oligohydramnios or anhydramnios.
- Chest size and suspected pulmonary hypoplasia.
- Other urogenital anomalies.
- Other major congenital anomalies in other organ systems eg. cardiac anomalies.
- Soft markers for aneuploidy.

Definitions

Cases were categorized as either (a) isolated or (b) isolated with marker or (c) complex depending on the prenatal ultrasound findings of LUTO and associated findings.

- Isolated LUTO was defined as findings of obstructive uropathy only.
- Isolated LUTO with marker was defined as findings of obstructive uropathy with additional soft marker (eg. nuchal oedema) on ultrasound.

- Complex LUTO was defined as obstructive uropathy with one or more additional structural anomalies or additional findings not related to the uropathy.

All cases were reviewed objectively postnatally and reclassified as either Isolated or Complex, to determine if the postnatal clinical information resulted in a change in the classification category. It should be noted that if a chromosomal anomaly was detected prenatally that this was not used to modify the classification.

4.5.2 Postnatal data

Outcome data was collected to assess survival, specific etiology and morbidity.

Survival data included information on

- Termination of Pregnancy (TOP)
- Intra uterine deaths (IUD) / or early fetal loss <28 weeks
- Stillbirths
- Neonatal deaths
- Infant deaths
- Alive beyond 1 year

Final diagnoses reflecting the etiology of the prenatal LUTO were classified as:

- Posterior urethral valve
- Presumed Posterior urethral valve
- Urethral stenosis
- Urethral atresia
- Prune Belly Syndrome
- Chromosomal anomaly
- Multiple congenital anomaly
- Cloacal anomaly
- LUTO unspecified

PUV is by far the commonest cause of LUTO in males but in our circumstances can be difficult to confirm with certainty. A category called Presumed PUV (PPUV) was used for cases where a diagnosis of PUV was suspected but not confirmed. These cases were either TOP's with no postmortem and only macroscopic examination of the fetus, or a postmortem may have found obstructive uropathy signs and no specific PUV or any other cause eg. UA/US/PBS/MCA/chromosomal/cloacal. The following criteria had to be rigorously met before a case was assigned as PPUV, and if a case did not meet the criteria, the final outcome was assigned as LUTO unspecified:

- male, final classification as isolated LUTO, no MCA, no chromosomal anomaly

Cases were classified as 'LUTO unspecified' if PUV was excluded postnatally and there was definite obstructive uropathy on postnatal investigations, in the absence of findings of a specific cause that would allow classification in the existing groups. An example is a case with thickwalled or floppy bladder, hydronephrosis, VUR, and no obstructive lesion found on MCUG or scope.

Morbidity data collected included information on postnatal urinary tract ultrasound findings if available; renal function data, surgery, urinary tract infection and bladder function. Postnatal renal ultrasound findings were correlated with prenatal findings. Surgery was studied relating to number of surgical procedures needed. Postnatal renal function were recorded as normal or impaired, with the creatinine level at age 1 year recorded if available.

4.6 Statistical analysis

Frequency ratios were calculated using the study population figures obtained from the Western Cape Provincial Department of Health as the denominator. Analysis was done with STATA statistical software v.13 (StataCorp, Texas) [51]. Associations between categorical variables were examined by the Pearson chi-square test with $p<0.05$ considered statistically significant, or the Fisher exact if the number in a cell was less than 5.

5. RESULTS

5.1 Overall frequency

During the study period a total number of 75 cases were diagnosed with LUTO features on prenatal ultrasound (figure 2), comprising 74 singleton pregnancy and 1 twin pregnancy in which only one of the twin was affected. Denominator data, the total number of deliveries in the specific health facilities that refer to Tygerberg as a tertiary unit, was available for 3 consecutive years (2010, 2011, 2012) and frequency figures could be calculated for these years; respectively 0.8 per 10,000 (4/47,997); 0.9 per 10,000 (4/45,357); 1.9 per 10,000 (9/48,252). The average for this 3 year period was 1.2 per 10,000 (17/141,606). Over the 12 year period, as few as 2 and as many as 11 LUTO diagnoses was made per one year period, with an overall average of 6 LUTO diagnoses per year.

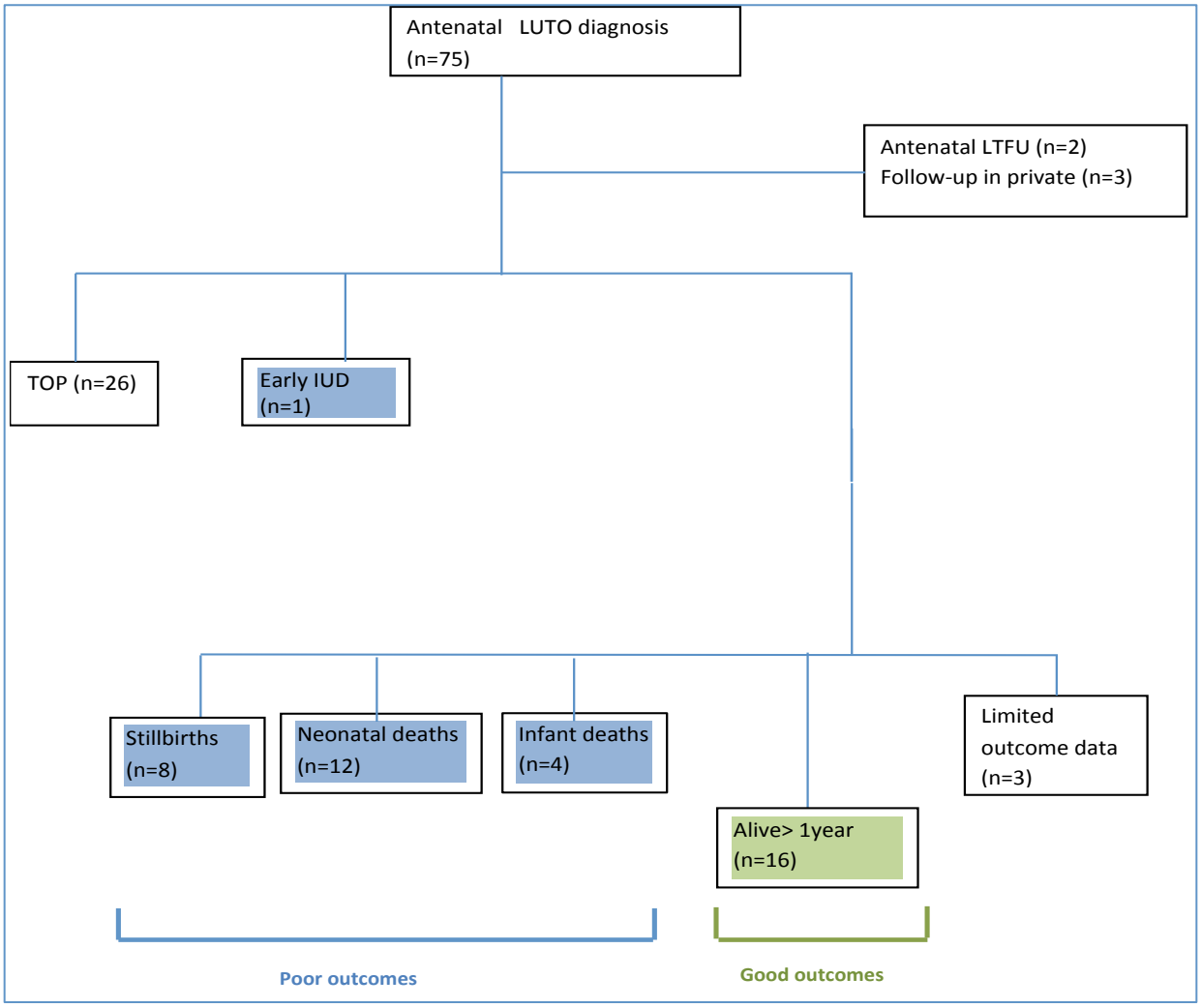


Figure 2: *Flow diagram of prenatal detected LUTO and outcomes*

5.2 Missing data

The final survival outcomes of a total of 7 cases were not known. Data on 5 prenatal cases were incomplete as 3 were followed-up in private with no final outcome information, and 2 cases defaulted prenatal care and no further information could be found regarding the outcome. In addition, three cases had incomplete outcome data, after they were lost to follow-up after a live birth. In one case the prenatal ultrasound findings were not known to the paediatricians and the child was discharged to a rural area with no investigations or follow-up. The 2nd case had renal investigations and was followed up until 4 months of age after which care was defaulted after a recent hospitalization. The 3rd case was a male with a resolving pattern of LUTO prenatally, a live birth with normal renal function in postnatal period. He was not followed-up and no information is available after the immediate postnatal period.

5.3 Description of prenatal findings

5.3.1 Demographics

The demographics of the cases presented in Table 8 show that the ethnicity of most cases was Coloured and almost a quarter of cases lived in rural areas.

Ethnicity	**n= 75**
Black African	23 (31%)
Coloured	48 (64%)
White	4 (5%)
Residence	**n=75**
Urban	35 (47%)
Peri-urban	22 (29%)
Rural	18 (24%)

Table 8: *Demographics*

5.3.2 Maternal age

The median maternal age was 27 years with a range of 15 to 44 years. 13% of pregnant women were of advanced maternal age (>35years).

5.3.3 Gestational age at diagnosis

The median gestation of prenatal LUTO diagnosis was 22.4 weeks (range 12.5w - 37.3w). Cases from rural areas were diagnosed at a median gestation of 22.2 weeks and urban cases at 23.4 weeks.

5.3.4 Isolated and complex LUTO

Of the total LUTO cases, 39 (52%) were classified prenatally as 'Isolated', 16 (21%) as 'Isolated with marker' and 20 (27%) as 'Complex'. Postnatal review of the LUTO classification showed that 46/69 (67%) was 'Isolated' and 22/69 (32%) 'Complex' (Table 9). Due to limited information 7 cases could not be classified postnatally, their prenatal classification was 2 'Isolated', 4 'Isolated with marker', and 1 'Complex'. The variation between the prenatal and postnatal classification is also presented in Table 9. The details of the 3 prenatal 'Isolated with marker' cases which became 'Complex LUTO' postnatally - 1 case had a normal female karyotype, had a cloacal anomaly and died on Day 6; the 2nd case with a 46,XY karyotype, was found after TOP on PM to have MCA (Ectrodactyly-ectodermal dysplasia-clefting syndrome); the 3rd case had a TOP and the postnatal karyotype showed a male Down syndrome genotype (47,XY, +21).

Prenatal classification n=75		**Postnatal clinical re-classification n=75**		**Variation between prenatal and postnatal classification**
Isolated	39	**Isolated**	46	-1 Isolated became Complex +1 Complex became Isolated +9 Isolated with marker became Isolated - 2 remained unclassified Total=39-1+1+9 -2=**46**
Isolated with marker (IM)	16			9 became Isolated 3 became Complex 4 remain unclassified
Complex	20	**Complex**	22	-1 Complex became Isolated +1 Isolated became Complex +3 Isolated with marker became Complex -1 remain unclassified Total=20-1+1+3-1=**22**
		Limited postnatal info	7	2 was Isolated 4 was Isolated with marker 1 was Complex

Table 9: *'Isolated' and 'Complex LUTO'*

5.3.5 Gender

The gender was known in 68 cases, in 1 additional case the genitalia was ambiguous, and the gender was not known or unspecified in 6 cases. A total of 60 males (60/68, 88%) and 8 females (8/68, 12%) had an prenatal LUTO diagnosis, resulting in a M:F ratio of 7.5:1. Prenatal classification showed that females had mostly 'Complex LUTO' (prenatal 5/8, 63%) and the majority of males had 'Isolated LUTO' (prenatal 36/60, 60%). For the prenatal 'Isolated with marker group', the gender distribution was as follows: 13/60 (22%) males and 2/8 (25%) females.

The postnatal classification showed 6/8 (75%) females had 'Complex LUTO', and in males a classification could be made in 55 cases, with 43/55 (78%) 'Isolated' and 12/55 (22%) 'Complex'. Two females had 'Isolated LUTO' on postnatal classification, 1 case had a normal karyotype and clinically PBS, no other anomalies, renal failure postnatallly and died in the neonatal period, no postmortem was done. The second female was classified as LUTO unspecified, as postnatal ultrasound showed circumferential bladder wall thickening with normal upper tracts. She had no anomalies, normal head ultrasound, normal spinal ultrasound, no karyotype was done.

5.3.6 Specific LUTO etiologies

	Total n=75	Prenatal			Postnatal			Male n=60	Female n=8	Unk/ amb n=7
		I	IM	C	I	C	?			
PUV	11 (15%)	9	1	1	11	0	-	11	0	-
PPUV	27 (36%)	20	7	0	22	0	5	27	0	-
PBS	6 (8%)	4	2	0	6	0	-	5	1	-
UA	1 (1%)	0	0	1	0	1	-	1	0	-
Luto Unspecified	8 (11%)	4	3	1	6	0	2	4	1	3
Chromosomal	7 (9.3%)	0	1	6	0	7	-	7	0	-
MCA	10(13.3%)	0	1	9	0	10	-	4	4	2
Cloacal anomaly	4 (5.3%)	1	1	2	0	4	-	0	2	2
Other: 1 resolving LUTO	1 (1%)	1	0	0	1	0	-	1	0	-
I = Isolated IM = Isolated with Marker C = Complex										

Table 10: *LUTO etiologies*

Table 10 shows the different underlying etiologies. PUV and PPUV was the most common underlying etiology in 38/75 (51%) of cases, all male [38/60 (63%) of males]. There were no cases of urethral stenosis.

5.3.7 Chromosomal anomalies

Karyotype or Aneuploidy analysis (FISH/qPCR) was done in 44 cases (44/75,57%), and showed a normal result in 34 cases and failed in 3 cases (Table 11). A total of 7 chromosomal anomalies, 9.3% of the total LUTO diagnoses, were detected. The details of the chromosomal anomaly cases are tabled in Table 12. Down syndrome was the most common chromosomal anomaly detected, in 4/7 (57%) cases. The mean maternal age of chromosomal anomaly cases was 32 years. Six out of the 7 cases were classified as 'Complex LUTO' after the first ultrasound, however 1 case did not have any specific congenital or structural anomaly, but was classified as 'Isolated LUTO with marker', due to an abnormal nuchal measurement. The case was confirmed to be Down syndrome after TOP and postnatal karyotype. Therefore, a chromosome abnormality was detected in 1 of 55 (1.8%, 95% CI= 0.01%-10.5%) that were not considered 'Complex' on prenatal assessment, and in 6 of 20 (30.0%, 95% CI = 16.2%-48.5%) that were 'Complex'. Thirteen of the 20 prenatal 'Complex' cases had a chromosome analysis, of which 6 (6/13, 46.2%) had an abnormal result.

	Chromosome analysis	**Results obtained**	**Chomosomes abnormal**
Isolated	19	17	None
Isolated with marker	11	11	1 (1xTrisomy 21 male)
Complex	14	13	6 (2x Trisomy 21 male) (1x FISH 21 male) (2x Trisomy 18 male) (1x Trisomy 13 male)

Table 11: *Chromosome analysis data*

Karyotype	**GA at diagnosis**	**Maternal age**	**Associated U/S findings**	**Complex LUTO**	**Outcome**
47,XY,+21	23.1	29	AVSD, nuchal oedema, talipes	Complex	TOP
47,XY,+21	16.4	43	Nuchal, Tetralogy of Fallot	Complex	TOP
47,XY,+21	26.5	39	Nuchal, pericardial effusion, abnormal placenta	Isolated with marker	TOP
47,XY+21	23.5	22	AVSD, nuchal	Complex	TOP
47,XY,+18	15.3	35	AVSD, talipes	Complex	NND
47,XY,+18	21.6	25	TOF, dilated CM, hypoplastic nasal bone, talipes, cord cysts	Complex	TOP
47,XY,+13	23.2	34	AVSD, cord cysts, micrognathia	Complex	TOP

Table 12: *Chromosomal anomalies*

5.3.8 Congenital anomalies

By organ system, the following congenital anomalies were noted in addition to LUTO features on pre or postnatal examination and investigations: Congenital cardiac anomalies were the most common (10 cases), followed by skeletal anomalies (3), cleft lip and palate (1). The cloacal anomalies in the 4 cases were quite complex, varying from complete ambiguous genitalia with no internal reproductive organs, to a common urogenital sinus.

5.3.9 Postmortem pathology

A postmortem examination was conducted in 12 cases, and a diagnosis was confirmed in 3 cases (UA =3, EEC=1) (Table 13). Even when the suspicion of underlying PUV was very high, it was never confirmed on postmortem. The postmortem was particularly informative in female cases with complex LUTO with multiple other anomalies.

- Male, TOP, 47,XY,+21. Urethral obstruction, with enlarged bladder, bilateral hydronephrosis and mild renal dysplasia, no microscopic obstruction could be demonstrated in urethra, diffuse bilateral pulmonary lymphangiectasia.
- Male, TOP, 47,XY,+13. Urethral atresia.
- Male, TOP, 47,XY,+21. AVSD, no PUV seen, however urethral obstruction.
- Male, TOP, 46,XX. Ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC), urinary obstruction distal to the bladder.
- Male, SB. Anus atresia, urethral atresia, absent urethral opening.
- Female, SB, 46,XX. Hydrops, Dysmorphic, pulmonary hypoplasia, TGA, Anterior abdominal wall defect, bowel malrotation, bilateral renomegaly, megacystis, vascular hamartoma in pelvis, short abnormal limbs.
- Male, TOP, 47,XY,+21. Urethral obstruction sequence with bilateral multicystic renal dysplasia, bilateral borderline pulmonary hypoplasia.
- Ambiguous, TOP. Cloaca, ambiguous genitalia, urethral atresia.
- Male, TOP. Urethral obstruction and bilateral cystic kidneys
- Male, TOP, 46,XY. Obstructive uropathy with hydroureter, secondary renal dysplasia, distal urethra not examined.
- Male, TOP, 46,XY. Lower urinary tract obstruction with hydro-ureter and hydronephrosis, distended bladder, hypoplastic lungs.
- Female, NND, 46,XX. Hydrops, imperforate anus, in utero bowel perforation, absent internal genitalia, obstructive uropathy.

Table 13: *Postmortem pathology*

5.3.10 Vesicocentesis

A vesicocentesis was done in 3 cases, all in male fetuses who had no additional anomalies on ultrasound. One case had a marker which increased the aneuploidy risk, the karyotype was normal male. None of the cases survived, 1 had a TOP and 2 were stillborn. Table 14 shows the pertinent findings.

	GAD	I/IM/ C	Amniotic fluid	Renal findings	Urine biochemistry	Outcome	Dx
Case 1	23.4	I	normal	No cystic changes	Na 76 Cl <70 K 3.1 osmolality 148 mosm/kg	TOP	PBS
Case 2	26.4	I	anhydramnios	Cortex mild echogenic not cystic	**At 26.6 weeks** Na 123 Cl 106 b2microglobulin 22.38mg/L osmolality 257 mosm/kg **At 27.3 weeks** Na 122 Cl 108 K 4.1 urea 4	SB	LUTO unspec 46,XY
Case 3	21.3	IM	Initial normal progressed to anhydramnios	Initial normal, progress to echogenic	**At 21.3 weeks** Na 74 Cl 62 K 2.4 Ca 0.6 Ca/creatinine ratio 3 b2microglobulin >3mg/L osmolality 164 mosm/kg **At 21.6weeks** Na 69 Cl 56 K 2.2 Ca 0.5 urea 9 b2microglobulin >3mg/L	SB	LUTO unspec 46,XY
Units- Na mmol/L K mmol/L Cl mmol/L Ca mg/dL urea mmol/L							

Table 14: *Vesicocentesis data*

5.3.11 Resolving LUTO diagnosis

In 1 case the prenatal suspicion of LUTO in a male fetus, classified as isolated, was based on findings of bilateral renal pelvis dilatation, unilateral echogenic renal cortex, dilated bladder at 21.1 weeks. Subsequent ultrasounds at 23.4 weeks found only mild bilateral renal pelvis dilatation and a normal bladder, and at 31.4 weeks unilateral moderate dilatation only. Postnatal evaluation showed a normal renal ultrasound and normal renal function. No information is available after the immediate postnatal period.

5.4 Survival outcomes

The survival outcomes are presented in figure 3; 26 (35%) had a TOP, 1 early IUD (1%), 8 Stillbirths (11%), 12 NND (16%), 4 Infant deaths (5%), 16 alive >1 year (21%), live birth with limited outcome data in 4%, no outcome data in 7%.

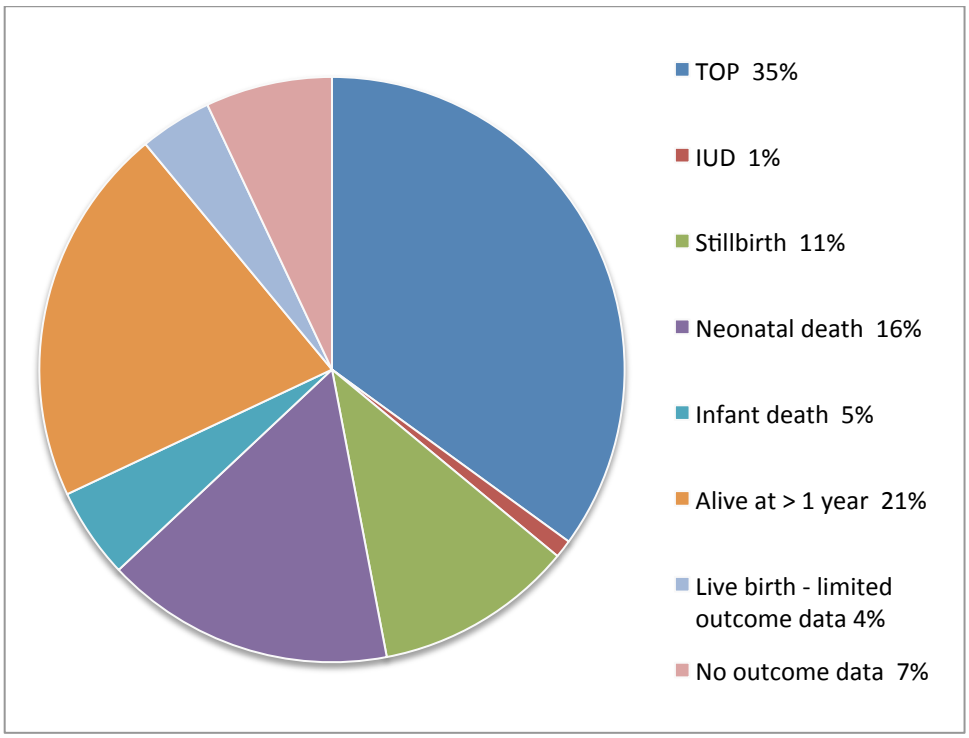


Figure 3: *Survival outcomes*

5.4.1 TOP and Feticide

A TOP was offered to 48 cases (48/75, 64%), and a TOP was done in 35% (26/75) of total LUTO cases. Of these 5 (19%) were late TOPs after 24 weeks and all of these were accompanied by a feticide procedure as per unit policy (19% of TOP and 6% of total LUTO).

The median gestation at feticide procedure was 26.1 weeks. The median gestation of LUTO diagnosis in the feticide cases were 25.6 weeks. In the cases where a TOP or feticide was offered and declined the outcome was a stillbirth or neonatal death in 19 of 22 (86%). Of the three cases surviving the neonatal period: 1 was an infant death at 4 months, 1 female case is alive with multiple disabilities, and 1 male case is alive at 6 years with a diagnosis of PUV and impaired renal function.

There was a trend toward TOP being less frequent in black Africans, with 4 (17%) of 23 choosing TOP compared to 22 (42%) of 52 Coloured or White individuals (p=0.06). Rural residents showed no difference in their decisions about TOP compared to urban/peri-urban residents, with 8 (44%) of 18 rural residence choosing TOP compared to 18 (32%) of 57 (p=0.32). All the TOP's were done for male fetuses.

The ultrasound data and LUTO classification of all the TOP'S are presented in table 15.

		TOP n=26 (100%)
Gender	Male	23 (88%)
	Female	0 (0%)
	Unknown	2 (8%)
	Ambiguous	1 (4%)
Gestation at diagnosis	Median	20.3 weeks
U/S Renal cortex	Cystic unilateral	6 (23%)
	Cystic bilateral	6 (23%)
	Echogenic bilateral	7 (27%)
U/S amniotic fluid	Oligohydramnios	8 (31%)
	Anhydramnios	10 (38%)
U/S pulmonary hypoplasia		10 (38%)
U/S bladder signs	Megacystis 1st trimester	1 (4%)
	Keyhole	9 (35%)
	Thickwalled	5 (19%)
Chromosomal anomaly		6 (23%)
Isolated/Complex	Prenatal: Isolated	13 (50%)
	Isolated with marker	6 (23%)
	Complex	7 (27%)
	Postnatal: Isolated	15 (58%)
	Complex	10 (38%)
	Unclassified	1 (4%)
LUTO aetiology	PPUV	14 (54%)
	PBS	1 (4%)
	Cloacal	1 (4%)
	LUTO unspecified	1 (4%)
	Chromosomal	6 (23%)
	MCA	3 (12%)

Table 15: *Findings in TOP cases*

5.4.2 IUD, stillbirth, neonatal and infant deaths

Spontaneous demise - including all IUD's, stillbirths, neonatal and infant deaths - added up to a total of 25 cases. The male:female ratio was 1:3.8, reflecting the higher relative proportion of females. In the prenatal period 11/25 (44%) had 'Isolated LUTO' and 60% had a final classification of 'Isolated LUTO'. The survival in the neonatal group was a median of 1.5 days

with a range of 1 to 28 days. Of the early neonatal deaths - 6 demised in the first day, 1 on day 2, and 2 in the first week. The remaining neonatal deaths occurred at day 11(1 case), day 14 (1 case with Trisomy 18), and in the 4th week of life (1 case, female with MCA). For the 4 deaths later in infancy, the average age of death was 4 months.

5.4.3 Survival >1 year

A total of 16 children survived past 1 year after a prenatal LUTO diagnosis. The majority were males with 'Isolated LUTO', PUV's were the most common diagnosis (8/16, 50%) and the median gestation at diagnosis was 25.5 weeks (range 19-36.1). The number of cases classified as 'Isolated LUTO' after ultrasound was 11/16 (69%), compared to 14/16 (88%) in postnatal period.

5.5 Prenatal prognostic indicators

The prenatal ultrasound features investigated as predictors of postnatal outcome are presented in tables 16-21. A 'Good outcome' group (defined as Survival > 1 year), was compared to 'Poor outcome group' (IUD, SB, NND, ID) and the TOP group. The prenatal findings shown to be significantly associated with a 'Poor outcome' are (a) bilateral renal cortex echogenic/cystic changes (p=0.029) b) anhydramnios (p=0.011) c) pulmonary hypoplasia (p=0.003).

The gestational age at diagnosis was found to be significant when comparing all 3 groups (p=0.015), however it was not found to be significant on comparison of the 'Good outcome' to 'Poor outcome group' (0.444) (Table 16).

Prenatal 'Isolated'/'Isolated with marker'/'Complex' classification showed no association when all 3 groups where compared (p=0.610), and when the 'Isolated with marker' (Im) group was combined with both the 'Isolated' (I) and 'Complex' (C) groups respectively, the analysis showed no significant association for 'Poor outcome' or 'Good outcome' (I+Im vs C p=0.365) (I vs Im+C p=0.289).

Other parameters that failed to show a significant association are gender (p=0.105), ethnicity (p=0.133), residence (p=0.866), postnatal 'Isolated'/'Complex' classification (p=0.246) and renal pelvis dilatation (p=0.925).

Gestation at Diagnosis	(1) Good outcome n=16	(2) Poor outcome n=11	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
< 24 weeks	7	14	22	0.444	**0.005**	**0.025**	**0.015**
> 24 weeks	9	11	4				

Table 16: *Analysis of Gestation at diagnosis as a prognostic factor*

Renal Cortex	(1) Good outcome n=16	(2) Poor outcome n=25	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
Bilateral normal	9	5	4	**0.030**	**0.006**	0.862	**0.029**
Unilateral normal	3	3	2				
Bilateral echogenic / cystic	4	16	17				
Unknown	0	1	3				

Table 17: *Analysis of Renal cortex findings as a prognostic factor*

Liquor	(1) Good outcome n=16	(2) Poor outcome n=25	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
Normal	14	12	9	**0.035**	**0.003**	0.302	**0.011**
Oligohydramnios	1	4	9				
Anhydramnios	1	9	8				

Table 18: *Analysis of Liquor findings as a prognostic factor*

Pulmonary Hypoplasia	(1) Good outcome n=16	(2) Poor outcome n=25	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
Normal	14	10	15	**0.001**	0.091	0.100	**0.003**
Mild	1	0	2				
Severe	1	15	9				

Table 19: *Analysis of Pulmonary Hypoplasia as a prognostic factor*

Isolated and complex	(1) Good outcome n=16	(2) Poor outcome n=25	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
Isolated	11	11	13	0.275	0.480	0.899	0.610
Isolated with marker	3	6	6				
Complex	2	8	7				

Table 20: *Analysis of presence of marker or 'Complex' LUTO (prenatally) as prognostic factors*

Gender	(1) Good outcome n=16	(2) Poor outcome n=25	(3) TOP n=26	1 vs 2 p-value	1 vs 3 p-value	2 vs 3 p-value	1vs2vs3 p-value
Male	14	19	23	0.805	0.177	0.05	0.105
Female	2	5	0				
Unknown	0	1	2				
Ambiguous	0	0	1				

Table 21: *Analysis of Gender as a prognostic factor*

The mortality was high in females, with 2/8 (25 %) alive at age 1 year; 1 SB, 4 NND, and 1 lost to follow-up at age 4 months, defaulted after a recent hospitalization with some complications.

5.6 Morbidity

Morbidity measures - renal function, surgeries, UTI, bladder dysfunction (enuresis requiring medication) - for the survivors past 1 year is detailed in table 22. The renal function, as measured by the serum creatinine at 1 year, was normal in 10/16 (63%). In the cases where information was available after the age of 1 year, the latest renal function was recorded as normal or abnormal. All cases with normal creatinine level at 1 year still had normal renal function until the latest follow-up, however none of the children are in their teens yet. Only in 1 case, with PBS, did an abnormal renal function at 1 year (documented at more than one occasion) improve with normal renal function in subsequent years. Ten (63%) cases had

surgery, 6 (38%) had multiple surgical procedures and 6 (38%) had no surgical procedure done. Nine cases (56%) had recurrent UTI's and 4 (25%) needed medication for enuresis.

5.7 Genetic counselling

Genetic counselling was provided by a trained genetic counsellor or geneticist to 50/ 75 (67%) cases and the remainder of the cases were counselled by the fetal medicine specialist. Some cases had a follow-up genetic counselling session during subsequent visits. Post-natal examination of stillborn or TOP cases were also done in 18 cases out of the 34 possible cases by a geneticist and the phenotypic information added to delineate the etiology and determine the recurrence risk that was then used to do postnatal counselling of couples.

ID	M/F	I/ Im / C	GAD	First Ultrasound			Worst Ultrasound			Final I/C	Diagnosis	Postnatal Renal Ultrasound	Last Renal function	Creatinine @1 year	Surgery	UTI	Bladder
				Renal cortex	Liquor	Lungs	Renal cortex	Liquor	Lungs								
2	M	I	32.4	N bil	N	N	N bil	N	N	I	LUTO unspec	Bil HN, no echo	Abn	Abn 61	-	-	-
3	M	Im	32.4	Bil ech	N	Mild PH	Bil ech	N	Mild PH	I	PUV	Bil HN, thin cortex	N	N 32	yes,2	yes	-
5	M	I	21.3	N bil	N	N	N bil	N	N	I	LUTO unspec		N	N 30	yes,1	yes	-
10	M	I	25.6	N uni	N	N	N uni	oligo	N	I	PUV	Uni non-functional	Abn	Abn 44	yes,2	yes	-
12	M	I	34.3	N uni	N	N	N uni	N	N	I	PUV	Bil HN	N	N 20	yes,2	yes	yes
15	M	C	27.5	N bil	N	N	N bil	N	N	C	MCA	Uni mild HN	N	N	-	-	-
25	M	I	36.1	Bil ech	N	N	Bil ech	N	N	I	PUV	Bil HN	Abn	Abn 54	yes,1	yes	-
33	M	I	20.4	N bil	N	N	Bil ech	oligo	N	I	PUV	Bil HN	Abn	Abn 41	yes,1	yes	-
39	M	I	20.1	Bil ech	N	N	Unkn	N	N	I	PBS	Bil severe HN	N	Abn 54	yes,2	yes	yes
42	M	I	33	Bil ech	anh	Severe PH	Bil ech	anh	Severe PH	I	PUV	Bil severe HN	Abn	Abn 54	yes,2	-	yes
43	M	I	19	N bil	N	N	N uni	N	N	I	PUV	Uni HN, other non-functional	N	N 23	yes	yes	-
48	F	C	20.1	N uni	oligo	N	N uni	oligo	N	C	MCA	Uni HN ech	N	N 25	-	-	-
57	M	I	35.4	N bil	N	N	Bil ech	N	N	I	PUV	Bil HN	N	N39	yes,3	yes	yes
58	M	I	21.6	N bil	N	N	N uni	N	N	I	LUTO unspec	Uni HN	N	N 32	-	-	-
70	F	IM	23.3	N bil	N	N	N bil	N	N	I	LUTO unspec	Bil N	N	N	-	-	-
75	M	IM	25.4	N bil	N	N	N bil	N	N	I	PBS	Bil N	N	N 20	-	-	-

Abbreviation Key: Abn – Abnormal Anh- Anhydramnios Bil - Bilateral Dx – diagnosis Ech - Echogenic GAD- Gestation at diagnosis N – normal Oligo- Oligohydramnios PH - Pulmonary Hypoplasia Uni – Unilateral Unk – Unknown UTI – urinary tract infection

Table 22: *Prenatal, postnatal and morbidity data on survivors > 1 year*

6. DISCUSSION

This study, to the best of our knowledge, is the first detailed report of congenital LUTO with frequency and postnatal outcome data in South Africa, and likely Africa. It can now be used as a reference point, to understand the natural history of this particular congenital pathology and its prognosis in this local setting and positively direct management. Once fetal surgical interventions such as VAS are routinely used in this setting it will be valuable to compare new data to the current findings.

A comparison of our data with the literature is possible for only some data aspects as some published studies include LUTO diagnosed both in the prenatal and postnatal period and other studies focus solely on PUV's. Most of the recent publications also predominantly include antenatal LUTO who had fetal therapeutic interventions, which can also not be directly compared to our cohort. Because prenatal therapeutic interventions are not widely available with the South Africa public health service, this study follows the natural history of LUTO in the absence of such interventions.

6.1 Frequency

The frequency of LUTO in our population is approximately 1.2 per 10,000 births in this study. As the denominator data was available for only 3 of the 12 years this figure needs to be viewed as an estimate of the frequency in the whole period. Comparing this to prevalence figures in the literature (2.2 to 3.3 per 10,000) which mainly reflect first world European or North American populations, the shortfall may be attributed to a number of factors, namely a) routine ultrasound is not offered or readily available in all health settings b) late booking c) missed early diagnosis due to poor ultrasound technique by inadequately skilled, unsupervised ultrasonographers d) this study only reflect prenatal detected LUTO cases. For these reasons, our frequency can be considered an estimate of the 'minimum prevalence' for prenatally detectable LUTO. This figure however is encouraging as it suggest that a fair proportion of all LUTO are being detected prenatally in our setting, particularly if this detection rate is compared with Malin et al's prenatal detection rate of 66% [3].

6.2 Demographics

The mother's ethnicity and place of residence provide a baseline for future data to compare to and view trends, however due to the lack of denominator data it was not possible to calculate individual ethnic prevalence figures as discussed at length in the Malin study which found LUTO significantly associated with maternal ethnic group and deprivation [3]. Neither the ethnicity nor place of residence was associated with a 'Poor outcome' or 'Good outcome' as defined in this study.

6.3 Gestational age at diagnosis

The gestation at diagnosis (GAD) is influenced by late referral as well as the fact that LUTO of a less severe nature may present at a later gestational age. In our setting the median gestation of 22.4 weeks complicates invasive testing, as a karyotype on amniotic fluid has a turnaround time of 2 weeks, and a result will likely be out after the 24 week gestation. This late gestation has implications for TOP and need for feticide. Comparing this study's GAD to the reported mean GAD of 19 weeks in a UK publication, it clearly shows that LUTO is diagnosed late in our setting [2]. An unexpected and unexplained finding in this study was that rural LUTO cases presented 1 week earlier than urban cases. This may reflect different ultrasound practices at different institutions, different pregnancy booking patterns or referral patterns.

6.4 Isolated / Complex

No prenatal LUTO ultrasound feature can reliably indicate the specific etiology therefore classifying cases as either Isolated or Complex is thought to stratify cases for prognostication and guide investigations. Most studies do not group cases formally into groups, so the 2 groups used by Malin was a unique report [3]. In our study we found it worthwhile to distinguish a 3rd group ('Isolated with marker') as we did not feel that the cases in this group fitted either of the other groups perfectly. Even though the majority of 'Isolated with marker' became 'Isolated' postnatally (9/17) (53%), one could not reliably predict which case would become 'Complex' based on gender or any other findings. In contrast, where a prenatal assessment of 'Isolated' (without marker) or 'Complex' LUTO was made, there was little shift from one category to any postnatally.

The comparison of this study's classification with the literature shows similar figures – Total prenatal 'Isolated' LUTO (73%) (combining the prenatal 'Isolated' and 'Isolated with marker') and prenatal 'Complex LUTO' (27%) in this setting vs. Malin et al 'Isolated' (77%) 'Complex' (22.2%) [3]. It remains to see how valuable and informative a classification into 'Isolated LUTO' and 'Complex LUTO' really is in the prognostic counselling process; it was shown not to significantly distinguish between the 'Poor outcome' and 'Good outcome' groups in our study, even when the 'Isolated with marker' group was combined with the other groups. The 'Complex' group did have a much higher chromosomal anomaly rate than the 'Isolated group', 30% versus 1%. This is expected as multiple congenital abnormalities of any sort have a high association with chromosome abnormalities.

6.5 Gender

The gender ratios in this study reflect the well-known predominance of male gender in LUTO as a result of the fact that PUV occurs exclusively in males [3]. Females did have complex LUTO in most cases (66% prenatal, 75% postnatal).

6.6 Specific LUTO etiologies

The specific etiologies in our study showed that PUV is the most common etiology of LUTO in our setting, similar to other reports in the literature [8]. For this study a PPUV group was distinguished in order not to group most cases as LUTO unspecified. Combining the PPUV and PUV groups equalled 51%, which is close to the 63% PUV rate Malin et al reported [3]. This study specified the LUTO etiologies in more detail than some other publications, therefore a direct comparison of figures is not possible for all etiologies. No cases had confirmed urethral stenosis, which is reported in 7% of LUTO in the literature, which may reflect the subtlety of the diagnosis and our setting's difficulty with diagnostic postmortem examinations [3]. This study supports the reported conclusion that the specific LUTO etiology cannot be determined with certainty in the prenatal period as the ultrasound features of all LUTO are similar [32].

6.7 Chromosomal anomalies

The rationale for karyotyping in prenatal LUTO includes looking for a chromosomal cause and specifying gender, as gender and other anomalies may not be visualised adequately with oligohydramnios [18]. It is even recommended that a CVS is done if there is markedly reduced liquor and amniocentesis is not possible. A male fetus with a normal karyotype likely has PUV, whereas in a female fetus suspicion of a more complex anomaly must always still be kept in mind [15]. Karyotype analysis was done in over half of the cases in this study (56%). It does involve an invasive test with a miscarriage risk, and therefore may not be acceptable to all couples, especially if it is not a curative procedure. This study reports a higher chromosomal rate (9.3%) than Malin et al (5.6%) [3]. Down syndrome was also the most common trisomy found in this study, in contrast to other studies reporting Trisomy 18 as the most prevalent chromosomal anomaly in LUTO [3]. This difference between this setting and the European data may be explained by the different Trisomy 21 screening practices. Europe has extensive first trimester screening for Trisomy 21, therefore most Trisomy 21 cases would have already been detected and offered TOP at 13 weeks before LUTO is even suspected, whereas first trimester screening is not universally offered or performed due to late booking in this setting. The percentage of women of advanced maternal age (older than 35 years) in this study was 13%, which in addition to other factors contributes to the higher rate of congenital anomalies such as LUTO and chromosomal anomalies in this setting. All the chromosomal anomalies were also detected in males, which is similar to a report by Al-

Hazmi that there is a gender difference in LUTO chromosomal anomalies [10]. This is an interesting finding that has not been reported in the rest of the LUTO literature. This may be related to the fact that most LUTO occur in males and the complexities of the embryological development of the bladder outlet structures in males may make it more susceptible to malformation.

The low detection rate in truly isolated cases of LUTO does raise the question of the cost-effectiveness of offering a prenatal karyotype analysis to a male with Isolated LUTO. Another reason why karyotype is considered is for fetal sexing, but it is unclear whether this has a practical benefit. The primary reason to consider invasive testing for this purpose would be if it is shown to affect prognosis. Our data do not demonstrate this, though the number of females is small. On the other hand, difficulty determining the fetal gender on ultrasound is likely to be due to anhydramnios or oligohydramnios – which are both are already indications of poor prognosis.

6.8 Postmortem findings

Postmortem autopsies in very premature fetuses are challenging and in our study we have not had any success in demonstrating PUV's clinically on a postmortem even in cases that were clinically very suggestive. This is in contrast to publications documenting conclusive diagnoses and distinguishing reliably between PUV, urethral stenosis and atresia [16]. It may be that our pathologists are not sufficiently experienced in this type of examination, or by its nature, being a dynamic valve–like structure, it may really be difficult to prove in a fetus without the aid of a cystogram. This raises the question if a postmortem is of great value in our setting, if we have to consider cost-effectiveness of diagnostic measures. The postmortems were definitely of value in 'Complex' cases to determine the extent of MCA or cloacal anomalies. A diagnosis of Ectrodactyly-ectodermal dysplasia and clefting (EEC) was made after a postmortem, a genetic condition with autosomal dominant inheritance and recurrence risk implications. EEC is associated with genitourinary anomalies, such as LUTO in 52% [52].

6.9 Survival outcomes

This study did show that survival is overall poor for prenatally detected LUTO. Comparing the survival outcome data with Malin et al – the survival data presented in the two figures (figure 1 and figure 3), show that this study had 10% more TOP's (35 % vs 24.6%), as well as more SB (11% vs 3.9%) more neonatal and infant deaths (21% vs 10.9%), but fewer alive at 1 year (21% vs 54%) [3]. The poor survival in our population may reflect other factors in addition to congenital LUTO severity that may be contributing to the higher mortality seen namely: a) prenatal factors such as less prenatal interventions eg. VAS b) postnatal factors such as less access to postnatal care, different approach to postnatal care eg. vesicostomy vs. primary

ablation of valves, lack of access to healthcare for ill-health related to LUTO, general high burden of infectious diseases (HIV, TB, TORCH infections, GIT and Respiratory illnesses) and preventable childhood illnesses, poor nutrition. Also a first-world prenatal ultrasound service will likely pick-up less severely affected cases, in contrast to a resource constraint setting where detection may be biased towards more severe cases, with resultant poorer overall survival and outcome. The poorer survival of children with LUTO in our circumstances has significant counselling implications.

6.10 Prognostic indicators

This study reports similar results to the literature regarding the prognostic prenatal ultrasound findings for LUTO [29,30]. It was not unexpected that decreased amniotic fluid, both oligohydramnios and anhydramnios, or bilateral renal cortex echogenicity / cystic changes or severe pulmonary hypoplasia would predict a 'Poor outcome', as these factors respectively implicate impaired renal function, severe late permanent renal changes and postnatal respiratory distress. The fact that this study's ultrasound findings are consistent with other centres, underscore the quality of the service amidst severe challenges. This study did not examine the predictive power of a combination of ultrasound factors (eg. amniotic fluid + pulmonary hypoplasia) and the sensitivity and specificity of such combinations. This may be worthwhile to explore as a specific combination of findings may further enhance prognostication by improving predictive accuracy as discussed in a publication by Oliveira [30].

Our data indicate that the chance of survival beyond 1 year of life was $\leq$20% if the ultrasound showed any one of the following: oligohydramnios or anhydramnios; severe pulmonary hypoplasia; bilateral renal echogenicity or cystic change.

Gender and the 'Isolated'/ 'Complex' classification was found not to be significant predictors of a 'Poor outcome', however the small numbers of females and 'Complex' cases likely influenced the statistical testing. As such, these are factors worth reviewing again if larger numbers are available.

Gestation at diagnosis (< 24 weeks or > 24 weeks) was not found to predict outcome in this study in non-terminated pregnancies, in agreement with some publications and the meta-analysis by Morris [29]. The gestation of diagnosis of course only reflects when the LUTO changes were noted for the first time on ultrasound and not the exact timing of onset of LUTO. This parameter would be influenced by when routine ultrasounds are done, with resultant wide variation between institutions which may in turn influence the significance of this parameter.

Other ultrasound findings such as renal pelvis dilatation did not achieve significance on analysis, consistent with the meta-analysis results from Morris [29].

6.11 Vesicocentesis

In our study, only 3 cases had a fetal urinalysis done by vesicocentesis. The reason for this low number is unknown. Malin also commented that it was uncommon for their cohort to have had fetal urinalysis done, and speculated that this was due to the growing evidence in the literature using renal cortex and amniotic fluid volume rather than fetal urine as more reliable prognostic indicators [3].

6.12 Morbidity

As the number of survivors past 1 year was only 16, conclusions should be made with caution until larger numbers are available to show statistically significant trends. Renal dysfunction, as measured by serum creatinine at age 1 year, was impaired in 37%. Serum creatinine is universally used as a marker of renal function, however a normal value does not imply normal renal function, as the level increases only when the GFR is <30%. It is still unclear on how the serum creatinine level correlates with the need for renal transplant in future [53,54,55]. This study does not have long-term follow-up and therefore cannot comment on long-term renal prognosis, which according to the literature is expected to be guarded [10,26,37]. A review of the survivors in this cohort in the future as well as collaboration with departments of Nephrology and Urology can hopefully provide evidence of the longterm prognosis and outcomes.

From this study data, multiple surgeries, enuresis and recurrent UTI's (with the risk to worsen renal function) are longterm problems survivors face in addition to impaired renal function. Morbidity involving bladder dysfunction (enuresis) is likely to be underestimated in young children who are not yet toilet trained.

6.13 Genetic counselling

The counselling aspect of a prenatal LUTO diagnosis is very important and can address a number of issues. In our study the majority of cases received counselling from a medical geneticist or genetic counsellor in addition to the fetal medicine specialist. This is a novel report, as this specific aspect has not been reported in other published studies on LUTO. This is a strength of this Fetal Medicine Unit, as this ensured that these cases were given adequate consultation time (a genetic counselling session typically lasts at least 30-45 minutes), balanced and unbiased information, risk information in an understandable format while received emotional support. This format ideally promotes client empowerment to make informed decisions and prepare the family to cope with the consequences of their decisions.

Even in the ideal counselling situation, there are some factors that will always have a negative impact on the session, such as uncertainty of outcome and prognosis. Uncertainty about predicted outcomes negatively affects both the counselling process and decision-making by the family. Making decisions regarding the outcome of a pregnancy causes significant stress, especially if TOP and feticide is offered. This study provides clear, locally relevant information for genetic counselling in local settings. It allows a more accurate estimation of fetal outcome, and the poorer overall outcome for LUTO in our setting should be kept in mind. It confirms that the poor prognostic factors are similar to those reported elsewhere. In addition it demonstrates the significant morbidity and burden of care even in good outcome cases.

There are a number of practical factors that may influence and impact on the counselling, decision-making and management of an antenatal diagnosis of LUTO that has not been assessed in this study and that would be useful to explore in subsequent research and in individual counselling scenarios e.g.: a) the lack of transport especially from rural areas at short notice when there is a need to attend numerous times and preferably with a partner b) the language barrier with lack of formal interpreters; c) limited education level with limited understanding of medical interventions and reduced decision-making capacity, contributing to the general disempowerment of patients.

The routine post-natal examination of all stillborn and TOP cases by the genetics department at Tygerberg Hospital adds an additional benefit to the management of prenatal LUTO. This continuity of care ensured that additional postnatal clinical information was available to infer a specific LUTO etiology that could then determine the specific recurrence risk to quote in postnatal counselling sessions of couples.

6.14 TOP and feticide

Termination of pregnancy by parental choice is a common outcome (24.6%) for prenatal detected LUTO, even in suspected isolated cases as reported by Malin et al [3]. A TOP was offered in 64% cases and accepted in 35% in this study. The reason why women choose to terminate a fetus for a severe congenital anomaly are varied - compassion for the child, self-interest and self-determination [47]. Cultural beliefs and religion may also play a role in the decision to have a TOP. In this study we did see a difference between the ethnic groups on analysis of the TOP data. A trend towards lower TOP rate was found in Black patients compared to the rest of the group. If confirmed, this may reflect different cultural views on TOP. We do not have religious information available in this cohort to explore other factors influencing decisions regarding TOP.

The data from this study shows that TOP was offered to cases with a genuinely poor prognostic outcome, as shown by the fact that in the prognostic indicator comparisons there

was no significant difference between group 2 ('Poor outcome') and 3 (TOP) (2vs3) for most of the parameters. The cases who were offered and declined late TOP and feticide also did poorly.

While this study identified the proportion of TOP's that included feticide to be 19% at an average gestation 26.1 weeks, there is little or no data to compare this to in the LUTO literature about the use of feticide and the gestational ages at the time of TOP. The ethics of TOP and feticide was discussed at length in the background section, in practice balancing the ethical principles can be complicated in a congenital anomaly scenario with the best outcome scenario in LUTO involving long-term chronic health problems and treatment like dialysis and renal transplants. The balance should always be in favour of preserving life, and balancing this with distributive justice in a resource constraint setting can be challenging and should ideally not be done on an ad-hoc basis, but in a systematic, multi-stakeholder approach. The current policy document on late TOP's was only developed after the period of this study and it would be interesting to review in future to see the impacts on this practice.

At a later gestation, lethality, pain and suffering and burden of care of the condition becomes increasingly important in deciding who would qualify for TOP. Therefore adequate knowledge of the natural history of both early and late onset LUTO has dual counselling benefits. Firstly, it can help determine the lethality and morbidity of the condition, to assist in who should be offered TOP, and if TOP not offered. And secondly, it can help emphasise the importance of monitoring; the need for early delivery; planning of delivery and immediate postnatal management to ensure optimal outcomes. Regarding the first point, this study shows that any single poor prognostic factor (oligohydramnios or anhydramnios; severe pulmonary hypoplasia; bilateral renal echogenicity or cystic change) results in poor outcome in >80% of cases. This suggests that it may be reasonable to offer late TOP with feticide to this group of women, especially since the few survivors are expected to experience significant pain and suffering e.g. from surgeries or renal dysfunction, with a considerable burden of care.

6.15 Challenges facing a fetal medicine clinic

The numerous challenges facing a fetal medicine clinic in South Africa are highlighted in this study on congenital LUTO; challenges such as the high burden of congenital anomalies such as LUTO in our country, the operator accuracy of measurements and technical skill, interpretation of findings and prediction of likely outcomes, ethical burden with issues like termination of pregnancy, feticide procedures. Facing these challenges and providing a competent service are enabled by clinical audits to develop practice policy and guidelines based on local population information that can assist with prenatal management decisions to provide clear guidance for clinicians and facilitate the difficult decision process for parents and ensure standardise practice.

7. CONCLUSION

This study shows that survival of prenatal detected LUTO is worse in our setting than described in developed world literature, however the reasons are uncertain, and likely multifold. The ultrasound prognostic indicators relating to outcome are similar to those previously described by other studies, decreased liquor, bilateral renal cortex involvement, and pulmonary hypoplasia. The implications for counselling are that even late TOP should be considered for congenital LUTO, except if there are no poor prognostic factors at all. There is currently no documented evidence to support the value of classifying LUTO into 'Isolated', 'Isolated with marker' and 'Complex' groups, however as it is non-invasive and relatively low cost, this promising stratification method should be explored further. In this setting, the detection rate of chromosomal anomalies was high in 'Complex' LUTO, but not in completely 'Isolated' LUTO, therefore a rational cost-effective approach to karyotype testing may include not performing karyotype analysis in prenatal 'Isolated' male cases.

This study provides novel data to add to the body of evidence on burden and impact of congenital anomalies in under-researched populations. Guidelines can now be developed using this data in conjunction with evidence-based information from the literature to direct genetic counselling and therapeutic decisions when presented with a prenatal diagnosis of LUTO. Not only do we recommend that severe prenatal renal tract dilatation should prompt thorough search for other major anomalies, but also for soft markers to better define the risk of underlying chromosomal anomalies that seem to be prevalent in our setting.

The study raised important ethical dilemmas faced by clinicians working in fetal medicine and supports the standardised application of guidelines concerning late termination of pregnancy.

Key recommendations
• Consider invasive prenatal testing for chromosome analysis in all 'Complex' and 'Isolated with marker LUTO' cases, however not in male with 'Isolated' LUTO
• Prompt evaluation for markers of Down syndrome in the presence of LUTO as Down syndrome is an under-recognised cause of LUTO
• LUTO in female is unlikely PUV, therefore search for other anomalies
• Parental counselling key information - morbidity is significant and many survivors develop CRF later in life

Issues to address	Practical recommendations
Late referrals	Feedback to MOU and clinics
Loss to follow up	Liaise with local clinics
Ethical issues	Policy to ensure equitable care
Information on long-term morbidity outcome (CRF, renal transplant)	Nephrology and Urology clinic audits

Funding

This research project did not receive any funding support.

Strengths and Limitations

Strengths:

- Prospectively collected data.
- Collected over significant time period.
- Follow-up data (fetal and paediatric) were found for most cases. Access to Paediatric Nephrology Clinic for follow-up data.
- Genetic team involvement both before and after delivery eg. fetal exam.

Limitations:

Accuracy of estimates of prevalence estimates depends on the accuracy of denominator data regarding the birth cohort over the past 12 years, and that data was only available for 3 year period.

The retrospective nature of the study meant that outcome data could not be verified for patients who were lost to follow-up.

This study did not have information on the outcomes of postnatal detected LUTO cases to compare the outcome differences if any between the two groups.

Reporting of results

The results of this study will be shared with the Department of Obstetrics and Gynaecology and the Department of Paediatrics. The results will also be submitted for publication in a peer review journal.

Appendices

A) Data capture sheet

B) Ethics approval

C) LUTO Clinico-diagnostic flowchart *(Tonni et al 2013 [20])*

D) LUTO algorithm of patient selection and evaluation for intervention *(Smith-Harrison et al 2015 [50])*

E) South African TOP Act 1996

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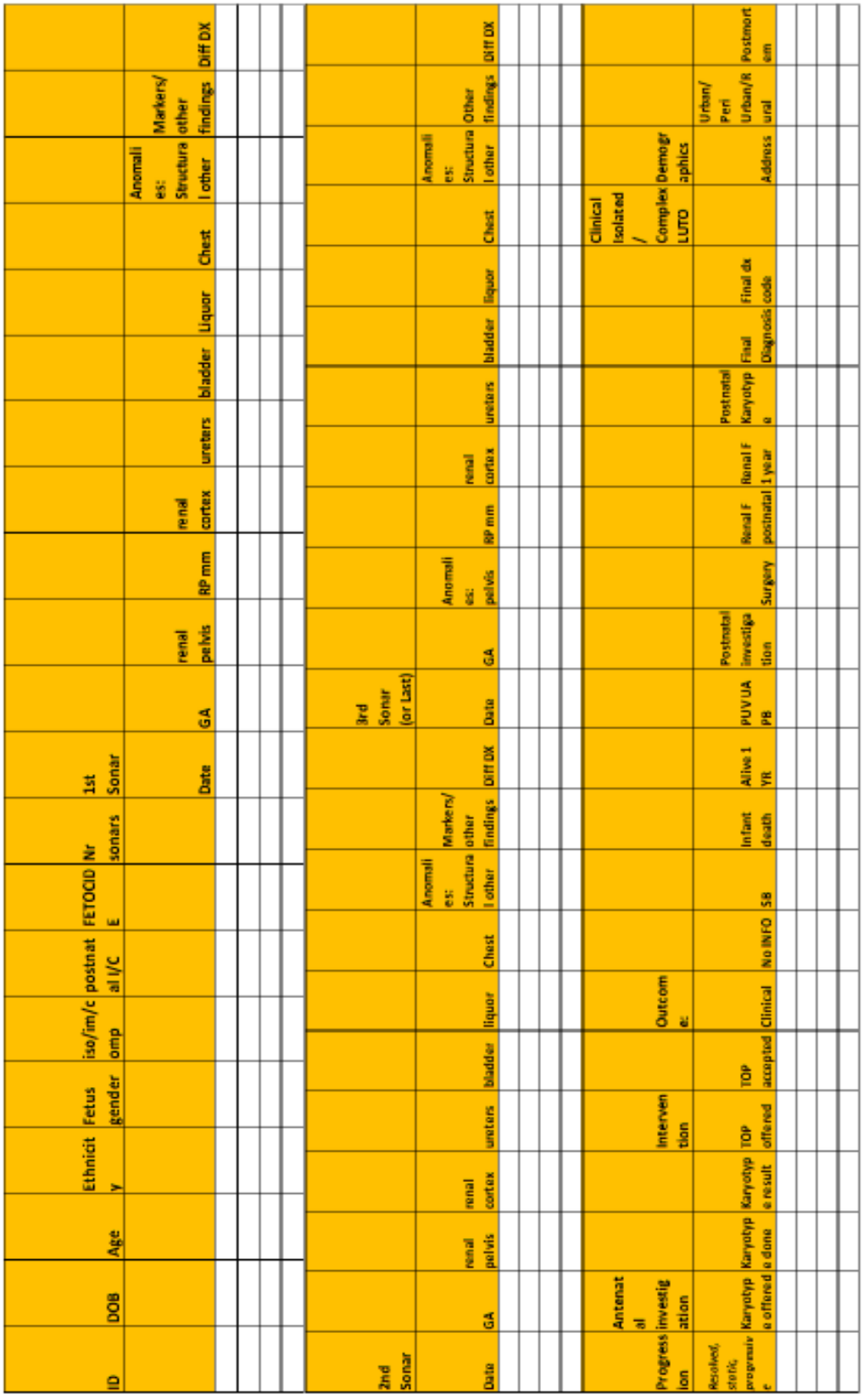
APPENDICES:

Appendix A: Data capture sheet



Appendix B: Ethics approval

UNIVERSITEIT·STELLENBOSCH·UNIVERSITY
jou kennisvennoot · your knowledge partner

Approval Notice
Response to Modifications- (New Application)

12-Sep-2013
Bezuidenhout, Heidre H

Ethics Reference #: N13/06/081

Title: **Prenatal diagnosis and outcome of congenital lower urinary tract obstruction(LUTO) at Tygerberg Hospital fetal medicine clinic :an audit of the past 10 years .**

Dear Doctor Heidre Bezuidenhout,

The **Response to Modifications** - ***(New Application)*** received on **10-Sep-2013**, was reviewed by members of **Health Research Ethics Committee 2** via Expedited review procedures on **11-Sep-2013** and was approved.
Please note the following information about your approved research protocol:

Protocol Approval Period: **12-Sep-2013 -12-Sep-2014**

Please remember to use your **protocol number** (**N13/06/081**) on any documents or correspondence with the HREC concerning your research protocol.

Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:
Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired.
The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit.
Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372
Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.
For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

Included Documents:
database
CORRECTIONS SYNOP
dec letter geerts
applic form
dec letter urban
cv geerts
synopsis
CORRECTIONS
cv urban
checklist

Appendix C: LUTO Clinico-diagnostic flowchart (*Tonni et al 2013* [20])

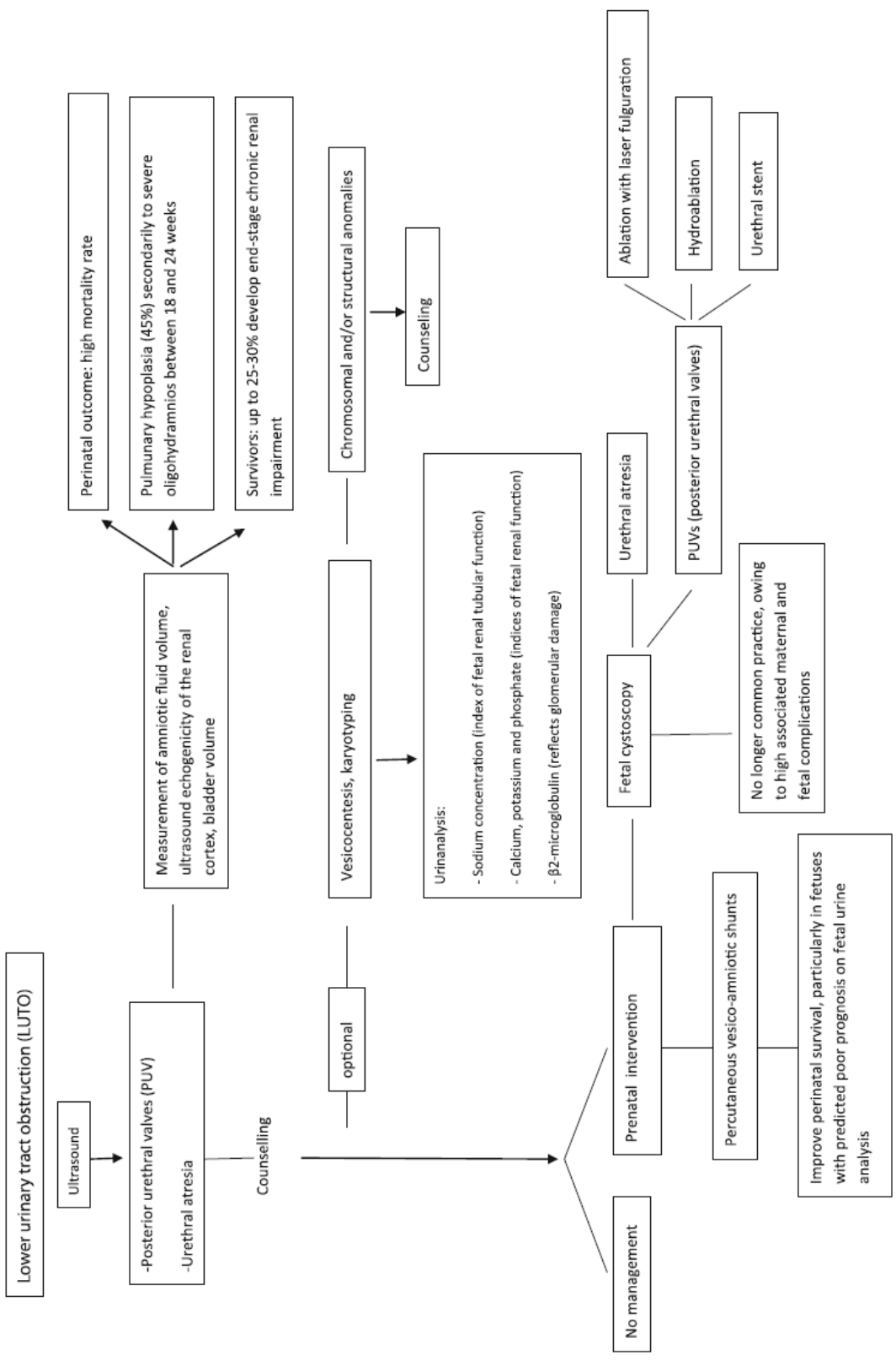
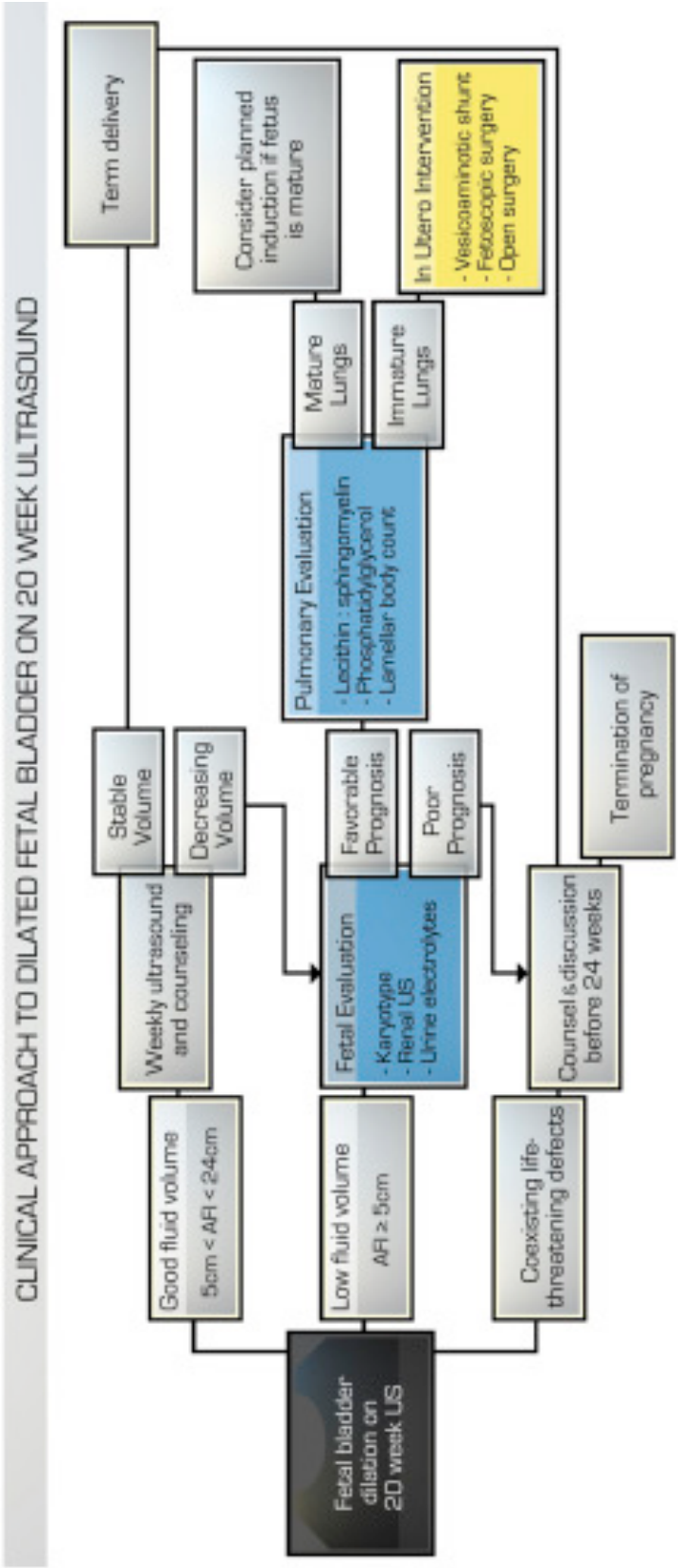


Fig. 4 Clinico-diagnostic flowchart to be used in the prenatal management of LUTO and when counselling parents regarding perinatal outcome

Appendix D: LUTO algorithm of patient selection and evaluation for intervention *(Smith-Harrison et al 2015 [50])*



Appendix E: South African TOP Act 1996

CHOICE ON TERMINATION OF PREGNANCY ACT, 1996.

PRESIDENT'S OFFICE

No. 1891. 22 November 1996

NO. 92 OF 1996: CHOICE ON TERMINATION OF PREGNANCY ACT, 1996.

It is hereby notified that the President has assented to the following Act which is hereby published for general information:-

ACT

To determine the circumstances in which and conditions under which the pregnancy of a woman may be terminated; and to provide for matters connected therewith.

(Afrikaans text signed by the President.)

(Assented to 12 November 1996.)

PREAMBLE

Recognising the values of human dignity, the achievement of equality, security of the person, non-racialism and non-sexism, and the advancement of human rights and freedoms which underlie a democratic South Africa;

Recognising that the Constitution protects the right of persons to make decisions concerning reproduction and to security in and control over their bodies;

Recognising that both women and men have the right to be informed of and to have access to safe, effective, affordable and acceptable methods of fertility regulation of their choice, and that women have the right of access to appropriate health care services to ensure safe pregnancy and childbirth;

Recognising that the decision to have children is fundamental to women's physical, psychological and social health and that universal access to reproductive health care services includes family planning and contraception, termination of pregnancy, as well

as sexuality education and counselling programmes and services;

Recognising that the State has the responsibility to provide reproductive health to all, and also to provide safe conditions under which the right of choice can be exercised without fear or harm;

Believing that termination of pregnancy is not a form of contraception or population control;

This Act therefore repeals the restrictive and inaccessible provisions of the Abortion and Sterilization Act, 1975 (Act No. 2 of 1975), and promotes reproductive rights and extends freedom of choice by affording every woman the right to choose whether to have an early, safe and legal termination of pregnancy according to her individual beliefs.

BE IT ENACTED by the Parliament of the Republic of South Africa, as follows:-

Definitions

1. In this Act, unless the context otherwise indicates-

(i) "Director-General" means the Director-General of Health; (iii)

(ii) "gestation period" means the period of pregnancy of a woman calculated from the first day of the menstrual period which in relation to the pregnancy is the last; (iv)

(iii) "incest" means sexual intercourse between two persons who are related to each other in a degree which precludes a lawful marriage between them; (ii)

(iv) "medical practitioner" means a person registered as such under the Medical, Dental and Supplementary Health Service Professions Act, 1974 (Act No. 56 of 1974); (v)

(v) "Minister" means the Minister of Health; (viii)

(vi) "minor" means any female person under the age of 18 years; (vii)

(vii) "prescribe" means prescribe by regulation under section 9; (x)

(viii) "rape" also includes statutory rape as referred to in sections 14 and 15 of the Sexual Offences Act, 1957 (Act No. 23 of 1957); (ix)

(ix) "registered midwife" means a person registered as such under the Nursing Act, 1978 (Act No. 50 of 1978); (vi)

(x) "termination of a pregnancy" means the separation and expulsion, by medical or surgical means, of the contents of the uterus of a pregnant woman; (i)

(xi) "woman" means any female person of any age. (xi)

Circumstances in which and conditions under which pregnancy may be terminated

2. (1) A pregnancy may be terminated-

(a) upon request of a woman during the first 12 weeks of the gestation period of her pregnancy;

(b) from the 13th up to and including the 20th week of the gestation period if a medical practitioner, after consultation with the pregnant woman, is of the opinion that-

(i) the continued pregnancy would pose a risk of injury to the woman's physical or mental health; or

(ii) there exists a substantial risk that the fetus would suffer from a severe physical or mental abnormality; or

(iii) the pregnancy resulted from rape or incest; or

(iv) the continued pregnancy would significantly affect the social or economic circumstances of the woman; or

(c) after the 20th week of the gestation period if a medical practitioner, after consultation with another medical practitioner or a registered midwife, is of the opinion that the continued pregnancy-

(i) would endanger the woman's life;

(ii) would result in a severe malformation of the fetus; or

(iii) would pose a risk of injury to the fetus.

(2) The termination of a pregnancy may only be carried out by a medical practitioner, except for a pregnancy referred to in subsection (])(a), which may also be carried out by a registered midwife who has completed the prescribed training course.

Place where surgical termination of pregnancy may take place

3. (1) The surgical termination of a pregnancy may take place only at a facility designated by the Minister by notice in the Gazette for that purpose under subsection (2).

(2) The Minister may designate any facility for the purpose contemplated in subsection (1), subject to such conditions and requirements as he or she may consider necessary or expedient for achieving the objects of this Act,

(3) The Minister may withdraw any designation under this section after giving 14 days' prior notice of such withdrawal in the Gazette.

Counselling

4. The State shall promote the provision of non-mandatory and non-directive counselling, before and after the termination of a pregnancy.

Consent

5. (1) Subject to the provisions of subsections (4) and (5), the termination of a pregnancy may only take place with the informed consent of the pregnant woman.

(2) Notwithstanding any other law or the common law, but subject to the provisions of subsections (4) and (5), no consent other than that of the pregnant woman shall be required for the termination of a pregnancy.

(3) In the case of a pregnant minor, a medical practitioner or a registered midwife, as

the case may be, shall advise such minor to consult with her parents, guardian, family members or friends before the pregnancy is terminated: Provided that the termination of the pregnancy shall not be denied because such minor chooses not to consult them.

(4) Subject to the provisions of subsection (5), in the case where a woman is-

(a) severely mentally disabled to such an extent that she is completely incapable of understanding and appreciating the nature or consequences of a termination of her pregnancy; or

(b) in a state of continuous unconsciousness and there is no reasonable prospect that she will regain consciousness in time to request and to consent to the termination of her pregnancy in terms of section 2, her pregnancy may be terminated during the first 12 weeks of the gestation period, or from the 13th up to and including the 20th week of the gestation period on the grounds set out in rection 2(1)(b)-

(i) upon the request of and with the consent of her natural guardian, spouse or legal guardian, as the case may be; or

(ii) if such persons cannot be found, upon the request and with the consent of her curator personae:

Provided that such pregnancy may not be terminated unless two medical practitioners or a medical practitioner and a registered midwife who has completed the prescribed training course consent thereto.

(5) Where two medical practitioners or a medical practitioner and a registered midwife who has completed the prescribed training course, are of the opinion that-

(a) during the period up to and including the 20th week of the gestation period of a pregnant woman referred to in subsection (4)(a) or (b)-

(i) the continued pregnancy would pose a risk of injury to the woman's physical or mental health; or

(ii) there exists a substantial risk that the fetus would suffer from a severe physical or mental abnormality; or

(b) after the 20th week of the gestation period of a pregnant woman referred to in subsection (4)(a) or (b), the continued pregnancy-

(i) would endanger the woman's life;

(ii) would result in a severe malformation of the fetus; or

(iii) would pose a risk of injury to the fetus, they may consent to the termination of the pregnancy of such woman after consulting her natural guardian, spouse, legal guardian or curator personae, as the case may be: Provided that the termination of the pregnancy shall not be denied if the natural guardian, spouse, legal guardian or curator personae, as the case may be, refuses to consent thereto.

Information concerning termination of pregnancy

6. A woman who in terms of section 2(1) requests a termination of pregnancy from a medical practitioner or a registered midwife, as the case may be, shall be informed of her rights under this Act by the person concerned.

Notification and keeping of records

7. (1) Any medical practitioner, or a registered midwife who has completed the prescribed training course, who terminates a pregnancy in terms of section 2(1)(a) or (b), shall record the prescribed information in the prescribed manner and give notice thereof to the person referred to in subsection (2).

(2) The person in charge of a facility referred to in section 3 or a person designated for such purpose, shall be notified as prescribed of every termination of a pregnancy carried out in that facility.

(3) The person in charge of a facility referred to in section 3, shall, within one month of the termination of a pregnancy at such facility, collate the prescribed information and

forward it by registered post confidentially to the Director-General: Provided that the name and address of a woman who has requested or obtained a termination of pregnancy, shall not be included in the prescribed information.

(4) The Director-General shall keep record of the prescribed information which he or she receives in terms of subsection (3).

(5) The identity of a woman who has requested or obtained a termination of pregnancy shall remain confidential at all times unless she herself chooses to disclose that information.

Delegation

8. (1) The Minister may, on such conditions as he or she may determine, in writing delegate to the Director-General or any other officer in the service of the State, any power confer-red upon the Minister by or under this Act, except the power referred to in section 9.

(2) The Director-General may, on such conditions as he or she may determine, in writing delegate to an officer in the service of the State, any power conferred upon the Director-General by or under this Act or delegated to him or her under subsection (1).

(3) The Minister or Director-General shall not be divested of any power delegated by him or her, and may amdnd or set aside any decision taken by a person in the exercise of any such power delegated to him or her.

Regulations

9. The Minister may make regulations relating to any matter which he or she may consider necessary or expedient to prescribe for achieving the objects of this Act.

Offences and penalties

10. (1) Any person who-

(a) is not a medical practitioner or a registered midwife who has completed the

prescribed training course and who performs the termination of a pregnancy referred to in section 2(1)(a);

(b) is not a medical practitioner and who performs the termination of a pregnancy referred to in section 2(1)(b) or (c); or

(c) prevents the lawful termination of a pregnancy or obstructs access to a facility for the termination of a pregnancy, shall be guilty of an offence and liable on conviction to a fine or to imprisonment for a period not exceeding 10 years.

(2) Any person who contravenes or fails to comply with any provision of section 7 shall be guilty of an offence and liable on conviction to a fine or to imprisonment for a period not exceeding six months.

Application of Act

11. (1) This Act shall apply to the whole of the national territory of the Republic.

(2) This Act shall repeal-

(a) the Act mentioned in columns one and two of the Schedule to the extent set out in the third column of the Schedule; and

(b) any law relating to the termination of pregnancy which applied in the territory of any entity which prior to the commencement of the Constitution of the Republic of South Africa, 1993 (Act No. 200 of 1993), possessed legislative authority with regard to the termination of a pregnancy.

Short title and commencement

12. This Act shall be called the Choice on Termination of Pregnancy Act, 1996, and shall come into operation on a date fixed by the President by proclamation in the Gazette.

SCHEDULE

No. and year of law

Short title	Extent of repeal
Act No.2 of 1975 Abortion and Sterilization Act, 1975	In so far as it relates to abortion